Massachusetts General Hospital, Boston, Massachusetts

MGH News

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# New Device Offers Added Protection for the Heart

LEON FRANK of Needham, MA, was sitting at home late one evening when he suddenly experienced what seemed like a big hiccup.

But it wasn't a hiccup at all. Mr. Frank's heart had begun to race, and a device implanted in his body was jolting his heart back to a normal rhythm.

"The jolt was over in an instant," he said. "I did not feel dizzy, sick, or weakened in any way."

Mr. Frank, who is 60, has suffered from coronary artery disease for years. Once or twice a year he has needed inpatient treatment for recurrent episodes of an overly rapid heartbeat, a form of arrhythmia or electrical pacing malfunction called ventricular tachycardia.

Since September, however, he has benefitted from what the Director of the MGH Arrhythmia Service describes as a "staggering leap in technology" over another type of implantable cardiac device that won federal approval only five years ago.

The new instrument, called Cadence, is presently undergoing investigational trials at the MGH and four other centers: Milwaukee County Hospital in Milwaukee, the University of Pennsylvania, Sequoia Hospital in Redwood City, CA., and Good Samaritan Hospital in Los Angeles.

Mr. Frank was the first MGH patient to receive implantation of the protective instrument. Dr. Jeremy N. Ruskin, head of the Arrhythmia Service, said that "we are absolutely delighted with what we have seen to date. All four patients in our clinical trial so far are doing extremely well."

He said his experience with other equipment and new technology has led him to expect trouble in the early phase of such clinical investigations and, he added, "I'm sure that there will be some surprises and probably some disturbing and unexpected observations, but our initial experience with this device has been extraordinarily favorable."

He added that the patients' psychological reaction has been exceptional.

"Since drugs they had taken were ineffective in controlling their arrhythmias," he said, "they had been afraid to do many of the things they once enjoyed, such as traveling. This device has changed that. Thus far, the patients feel free to be mobile. They're no longer dependent on high doses of very toxic drugs, and they don't have to worry about whether a hospital is close by."

The previously introduced heart support instrument, called an Automatic Implantable Cardioconverter Defibrillator (AICD), has saved many lives. It quickly shocks the heart to terminate either sudden irregular impulses in the organ's pumping chambers (ventricular fibrillation) or an attack of very rapid beats (ventricular tachycardia).

Without immediate intervention, ventricular fibrillation in particular can lead to quick circulatory failure and death.

"Although the AICD works extremely well, its limitation is that it is a high-energy device," Dr. Ruskin said. "It delivers a shock equal to its full energy

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# *Industrial Support Raises Research Hopes*

EVER SINCE antibiotics first appeared during World War II, saving countless lives, leading American medical centers have accorded high priority to research.

"The practice of medicine is clearly the application of knowledge toward practical ends," an MGH physician once said.

As the postwar surge of research gathered steam, the MGH's Committee on Research stressed the importance of undertaking both basic and applied studies.

"There is no clear dividing line," the committee said. "Basic research is aimed at increasing understanding, and applied research at utilizing this understanding to solve specific practical problems. The

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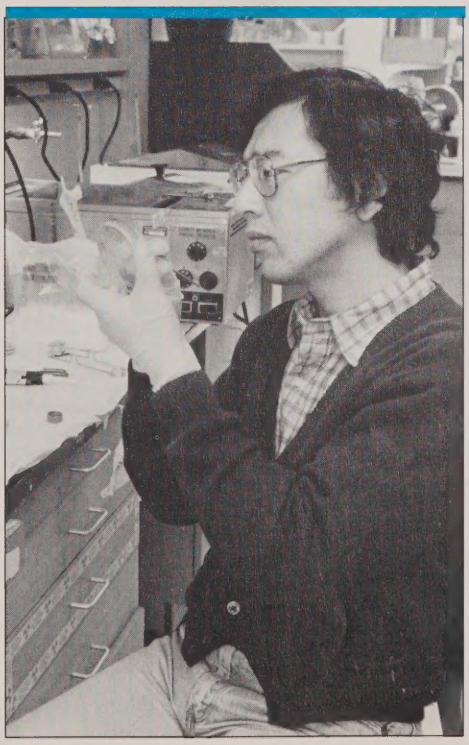

***Right:*** *In the Molecular Hepatology Laboratory of the MGH Cancer Center, Dr. Masaki Nishiyama of Tokyo is striving to isolate a gene that produces a liver cancer-associated protein. The center has recruited topflight scientists from throughout the world.*

## INSIDE:

**Page 7**—A new Medical Directive improves on living wills.

EDITORIAL

# Industrial Ties Need Academic Freedom

DOES INDUSTRIAL SUPPORT undermine the freedom of academic research? As industry funds more and more medical center studies, academicians worry about that possibility. That is understandable. Humans always fear whatever is so new that it leaves major questions unanswered. From fire to space flight important developments have often provoked the mind to imagine the worst. Relatively soon, though, we recognize that despite potential for misuse, most new tools provide more opportunity than danger.

When the federal government began pouring large sums into academic research, all sorts of wild predictions arose: Politicians would dictate research projects leaving universities and hospitals without the freedom to choose their own studies. Weaponry would become the major projects supported. The government would demand secrecy about the research. Politicians and bureaucrats would corrupt scientists. The government would fund frivolous research. No doubt it is possible to find examples of how each of these predictions became true. For the most part, however, the federal funding of research has reaped a harvest of major advances that have made American medicine—though not its costs—the envy of the world. For every American who goes outside the United States to seek care, there are many times more foreigners who come to this country for diagnosis and treatment.

Industry has long supported academic research. The agreement which opened the floodgates, however, came in 1981 when Hoechst A. G. granted $68 million (including $18 million for construction and equipment) to the MGH. Dire prophesies about that funding followed swiftly. Even though the MGH sought and Hoechst ultimately accepted language guaranteeing academic freedom, the Cassandras were strident.

Two and one-half years later, the New York Times magazine scrutinized how those freedoms were actually faring. The article concluded that for the MGH the agreement works but: "Massachusetts General Hospital is a powerful and prestigious institution . . . Other institutions may have a harder time preserving their independence against the interests of their benefactors."

The 1981 Hoechst agreement has been looked upon as a model. Even the strong language therein embodied does not by itself guarantee that it will work for the MGH or any other institution. There will always be failures. To make even an "ideal" arrangement become an ethical, academic success demands scientists and industrialists who are determined to make it a success. That is why rational concerns expressed even within the institutions which benefit can be positive. That very concern helps raise the determination to succeed.

# *New Heart Aid*

*(Continued from Page 1)*

capability,which is a million times that of the much more commonly used pacemaker.

"As patients who could benefit from devices such as an AICD were studied, it became clear that most tachycardias, particularly the ventricular form, can be terminated with much lower energies. The high energy shock emitted by an AICD was really intended to be an intervention of last resort."

Mr. Frank's "hiccup" would have felt more like a kick inside the chest if he had been wearing the implanted defibrillator. Instead of the l00-volt shock he received from the new device implanted in his abdominal wall, AICD would have delivered a jolt 20 times more intense.

Made by Ventritex of Sunnyvale, CA, the new instrument is roughly 3 3/4 inches high, 3 l/4 inches wide, and 7/8ths inch thick.

Dr. Ruskin, who is also Associate Professor of Medicine at Harvard Medical School, said a half dozen companies are developing instruments that will have capabilities similar to those of Cadence.

One of those companies is CPI (Cardiac Pacemakers, Inc., of St. Paul) which made the original AICD. CPI has already followed AICD with more versatile versions whose energy output can be programmed at various levels.

Cadence can be programmed to perform a series of specific functions, one at a time or all at once.

In addition to being a defibrillator, it can be set to detect two different types of ventricular tachycardias and then to deliver a wide range of individualized therapies for those conditions.

"For people who have recurrent ventricular tachycardias, and there are many,

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many thousands," Dr. Ruskin said, "we now have a device that can deliver pacing to terminate them and to deliver shocks only when and if the pacing doesn't work. The shock becomes a backup therapy."

The principle behind the pacing is that if the abnormally rapid heartbeat can be accelerated to an even faster pace, the "overdriving" can actually restore a normal sinus rhythm in most patients (*MGH News*, May 1985). It does so by actually penetrating the electrical circuit from which the arrhythmia is arising and interrupting it.

Dr. Ruskin sees the device as a treatment of choice for as many as 50,000 Americans a year who have been stricken with ventricular fibrillation or cardiac arrest. And, he said, there are probably another 50,000 patients a year with recurrent ventricular tachycardias who would benefit from the instrument.

*Dr. Ruskin sees the device as benefiting as many as 100,000 Americans a year who have been stricken with either ventricular fibrillation or ventricular tachycardias.*

It can also prevent excessive slowing of the heart (bradycardia). The MGH cardiologist explained that in some patients whose fast rhythms are stopped by antitachycardia pacing or defibrillation, abnormally slow rhythms ensue. This is a condition known as postcardioversion asystole.

"This is not a very common development," he said. "It happens maybe 10 percent of the time. The new device would protect against such an excessive slowing of the heart rhythm."

In addition to its therapeutic functions, the new system provides extremely sophisticated diagnostic information. It not only takes note of every arrhythmia that occurs but also stores data to inform the patient's doctor when the arrhythmias happened, how severe the disturbances were,

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*In the Cardiac Electrophysiology Laboratory, Bruce Laramee, RN, and Mary Guy, RN, prepare Leon Frank of Needham for tests to determine how well a new instrument implanted in his body is protecting his ailing heart.*

## Letter to the Editor

Dear Editor:

Thank you so very much for your feature article on Sudden Infant Death Syndrome (SIDS), which appeared in the November, '89, issue of MGH News.

I am encouraged to read that, as a result of their research, Dr. Dorothy Kelly and Dr. Daniel Shannon are narrowing the population of possible SIDS victims. It must be terribly frustrating to SIDS researchers, just as it is to SIDS parents, not to even know which babies to study for increased risk to die from SIDS. Because of this lack of a clear-cut, high-risk baby, studies such as those done at MGH will do much to begin to point out possible infant populations on which concentrated SIDS research should, and should not, focus.

Our group, as the only SIDS parent support group in Orange County, California, is especially appreciative of Drs. Kelly and Shannon's pioneering research work. Although not mentioned in this article, we are very interested in and supportive of Dr. Hannah Kinney's work on the brainstem and its role in SIDS.

In memory of our precious children who have died from SIDS, we encourage you to press forward with your research projects and will continue to support your efforts both monetarily and through prayer. We join you in KNOWING that one day the scourge of SIDS will be gone and no more families will grieve and suffer the devastation of a SIDS death. The personal commitments of your dedicated staffs tell us that you will soon be victorious.

Mrs. Lynne G. Trujillo, president
Guild for Infant Survival, Inc.
Orange County
Irvine, California

# *Research Funding Helps Area's Economy*

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latter cannot long proceed without advances in the former."

With industrial, governmental, foundation, and philanthropic support, the MGH has carried on a tradition of achievements in medicine and surgery, and it has also scored numerous breakthroughs in basic science to provide the groundwork for future solutions to health care problems.

Recent years have seen industry supporting MGH studies on a large scale.

Last month, the hospital and one of the nation's leading pharmaceutical companies, Bristol-Myers Squibb, announced the signing of a five-year, $29.7 million pact for the establishment of a Cardiovascular Research Center (CVRC) in the MGH Cardiac Unit.

Investigators will study the normal and disease functions of the cardiovascular system, its regulation, and the diagnosis and treatment of disorders of the system.

The hospital will name a CVRC Director, who will initiate and supervise the center's program. An international search is planned for topflight personnel to staff the new center.

Marvin Guthrie, Esq., Director of the MGH Office of Technology Affairs, said the hospital will hold title to any patents resulting from research discoveries, but Bristol-Myers Squibb will have an option for exclusive licensing rights on any products resulting from the discoveries. The MGH will be entitled to royalties on product sales.

Mr. Guthrie emphasized that these patent and licensing arrangements are exactly the same as those negotiated by the hospital under other major research agreements with industry.

Last August, the MGH's General Director, Dr. J. Robert Buchanan; its Chief of Dermatology, Dr. John A. Parrish; Mr. Guthrie, and the Dean of Harvard Medical School, Dr. Daniel C. Tosteson, flew to Tokyo for the signing of a 10-year, $85 million agreement between the hospital and a prominent Japanese pharmaceutical and cosmetic firm.

The pact with Shiseido Company, Limited, provides for the establishment and support of laboratories at the MGH to study skin. Dr. Parrish, who will be the first Director of the MGH-Harvard Cutaneous Biology Research Center, remarked:

"When you consider the importance of skin, it is relatively neglected by the most modern capabilities of basic research. The new center offers an exciting opportunity to get a running start into this critical area."

Dr. Buchanan said the fruits of the studies by the center's anticipated staff of 100 scientists and support personnel will ultimately benefit people all over the world.

"More immediately," he said, "this center will be a boost to the Massachusetts economy. New jobs and a major economic infusion will result. With the state's current fiscal problems, this major new funding will make a meaningful contribution."

The Shiseido signing coincided with talks to extend a pact between the MGH and Hoechst AG of Frankfurt, Germany, a major international chemical firm.

In 1981, a 10-year, $68-million dollar agreement with Hoechst paved the way for opening a new Department of Molecular Biology at the MGH under Howard M. Goodman, Ph.D., a renowned scientist, to conduct basic research.

Dr. Goodman's staff of some 120 scientists and other specialists has been very productive, advancing basic knowledge in many areas. The department has obtained or applied for well over 100 patents. As is typical with hospital research funded by industry, Hoechst has a right of first refusal to a license in these patents. However, because the studies seek general rather than specific knowledge, Hoechst has not as yet developed specific products from these discoveries.

*Harvard graduate student Pablo Guevara of Puerto Rico is trying to determine in the MGH's Molecular Biology Department whether a specific gene in bacteria is affecting the bacteria's ability to cause disease in a plant. Xinnian Dong, Ph.D., of Beijing, China, looks on.*

*The recipe for successful biomedical research has required three basic ingredients: people, space, and money.*

The recipe for successful biomedical research has required three basic ingredients: people, space, and money.

The MGH has never found it difficult to recruit outstanding investigators. Space has often been a problem, but prudent planning has usually met such challenges. As for money, it has generally been forthcoming but not without some criticism at times over the source of the funding.

After World War II, there were fears that academic freedoms would be jeopardized if institutions like the MGH, the first and largest teaching hospital affiliated with Harvard Medical School, accepted federal research grants. Critics felt that the government might try to dictate what projects the hospital should undertake and even how the studies should be conducted (*MGH News*, October 1987).

"Support from industry enabled the MGH to begin its research programs immediately after the war," said Dr.

Ronald W. Lamont-Havers, the hospital's Director of Research Affairs. "The government did not begin to award any grants of significance until the early 1950s."

As federal money was put to use, the earlier fears of losses of academic freedoms proved groundless.

Dr. Lamont-Havers, a former Acting Director of the National Institutes of Health, said that "everybody looked upon the 50s to mid 60s as a golden era in which the government funded practically every research application.

"The government was getting involved in ever increasing commitments, however, and began to realize by the late 60s that there just wasn't enough money to go around."

Even though the early 1970s saw an outpouring of federal aid to fight cancer and heart disease, the academic community became acutely aware of the overall instability of the government's largess.

"The hospital recognized the need to encourage interaction with industry," Dr. Lamont-Havers said. "This concept, in fact, was beginning to flow through all of academia. Indeed by the 1980s the federal government was advising even its own intramural research centers to look to industry for collaboration."

As grants from industry reached sizable proportions, concerns arose. The same fears over losses of freedoms that had plagued consideration of federal grants in the early days resurfaced. This time industrial support of medical research became the target of critics.

The MGH carefully protected academic freedoms when it signed the Hoechst pact in 1981. Dr. Goodman's department was assured the freedom to choose its own research projects, to collaborate with others, to write its own scientific articles, to decide when to write them, and to pick the journals in which to publish those reports. Similar provisions became a part of all subsequent MGH research arrangements with industrial sponsors.

Hoechst's long-range support not only provided the Molecular Biology Department with financial stability but also flexibility in that it could undertake experimental programs that were highly innovative and long-term but at the same time therefore especially uncertain to achieve results.

"Putting together a new idea or concept can take a long time," Dr. Goodman said. The Hoechst arrangement let his people move forward even after lengthy preliminary research. Renewal of, say, a three-year federal grant would have hinged on showing productive results from the earlier work and would have required scientists to spend months just to put forth a new grant proposal.

Among those wary of major industrial financing of medical research is Dr. Jerome Gross, Chief of the MGH's Developmental Biology Laboratory for more than 30 years. He left that post recently upon retiring from Harvard Medical School as Professor of Medicine Emeritus.

Dr. Gross fears the decreased availability of federal support and the increased difficulty in competing for a share of those funds will make offers of large chunks of industrial money seem more attractive to young researchers.

"It's much easier for them to think that that is the best way to go," he said. "They

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***Above:*** *With a torsion pendulum and laser light, Research Technician Jennifer Lamb measures the rigidity of muscle protein (actin) gel in the Hematology-Oncology Laboratory.*

***Below:*** *Research Technician Usha Varadarajan of India tends plants of the mustard family being cultivated in the Molecular Biology Department's greenhouse for use in a variety of laboratory experiments.*

# *Researchers Rely On Collaboration For Successes*

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wouldn't have to worry about the peer review system which decides who gets government aid and which, I might add, is still the best system anybody ever invented."

Support from industry boils down to a contract, Dr. Gross stated, and in many instances the companies want to dominate and direct the research if they can.

"At the MGH, we are quite fortunate to have a long history of independence which allows us to negotiate hard-nosed," he continued. "This hospital has made it clear in negotiations with others that 'if you won't respect our principles of academic freedom, then good-bye.'"

Ernest M. Haddad, Esq., General Counsel of the MGH, said that commercial sponsors of medical research almost always enter negotiations wanting to limit collaboration between their sponsored investigators and others engaged in similar research so as not to jeopardize exclusive rights to any new discovery.

"But the reason they put money into university and hospital research," he pointed out, "is that they see it as having more potential than the research they might do in their own laboratories.

"Scientists in academia succeed not by isolating themselves but by swapping information with colleagues and by publicizing their new knowledge in journal papers. That is why the growth of knowledge in these labs is so fertile ... so healthy.

"As a matter of principle, we would never agree in any negotiations to eliminate collaboration. It is a fundamental component of academic freedom and effective research."

Problems of finding space in which to conduct MGH research have paralleled the dramatic rise of biomedical studies since World War II.

"Every new building that rose on the MGH campus was quickly filled," said Ronald S. Newbower, Ph.D., Deputy Director of Research who on January 31st will become Associate General Director for Research and Technology Affairs.

"Today, medical research requires more space than ever. The work can't be tucked into nooks and crannies anymore. The increasingly sophisticated work that has to be done involves complex equipment."

The Molecular Biology Department occupies five upper floors of the Wellman Research Building which opened several years ago on the main MGH campus. Both the Cardiovascular Research Center made possible by the Bristol-Myers Squibb support and the Cutaneous Biology Research Center will be situated in the Lawrence E. Martin Laboratories in Building 149 of the Charlestown Navy Yard. The MGH moved into the eight-story structure less than two years ago expecting to use a few floors but wound up leasing the entire building last summer. That one building has more research space than the MGH accumulated since its founding in 1811.

Dr. Newbower said the building has floor space equalling the size of 13 football fields.

"Even though some interior portions of Building 149 are still under construction," Dr. Newbower said, "there is no area that is not already committed for one MGH purpose or another."

Mr. Guthrie said the CVRC will occupy about 75,000 square feet of space, more than 15 percent of all the research space. He said the designated area for the center on the fourth floor should be ready for occupancy within 14 months.

Work on the Cutaneous Biology Research Center on the third floor is expected to be completed next December. Meantime, its director, Dr. Parrish, has announced three key, two-year appointments for planning and recruiting. Dr. Lamont-Havers will be Deputy Director of the center while Drs. Gross and Howard Baden will serve as Acting Associate Directors for Research.

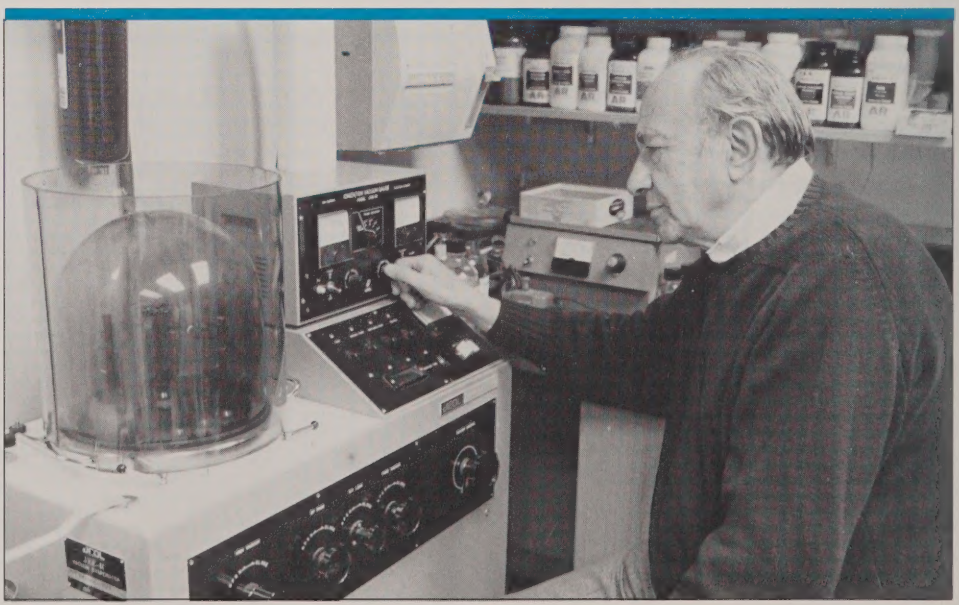
In its early years the new center will not focus on a specific dermatologic disorder but will serve primarily as a basic science unit studying the structure and function of skin. The Shiseido contract encourages the MGH to obtain added funding for the skin center from government and private sources.

"We're hoping to attract scientists who can generate their own research funds," Dr. Parrish said. "We will provide the environment and startup financing but after a certain protected period we will expect the investigators to begin bringing in a large portion of their needed money."

Mr. Guthrie emphasized that in the Shiseido agreement as well as all others in which exclusive licensing rights have already been pledged, the hospital will closely study any proposed funding from other sources to be sure it would not interfere with the licensing obligation.

Dr. Parrish, who is also Chairman of the Dermatology Department at Harvard Medical School, said Harvard and the MGH will each appoint two representatives to a scientific panel that will oversee the new skin center. The school will also manage a study program within the center for graduate and medical students.

Through support from industry, academic institutions like the MGH can continue to break ground, exploring and advancing new ideas with assurance that those having promise will not die on the vine or gather dust in the laboratory. ■



*Employing a technique called "shadow casting," Dr. Jerome Gross in the Developmental Biology Laboratory increases the contrast and depth of biological molecules so they can be examined in an electron microscope.*

# A New Medical Directive Improves on Living Wills

TWO BOSTON physicians have proposed a way for a person to specify medical care preferences in the event of a life-threatening illness or injury someday involving mental incompetence.

Called The Medical Directive, the advance care plan was devised by Dr. Linda L. Emanuel of the MGH and her husband, Dr. Ezekiel J. Emanuel of Beth Israel Hospital. The two internists described their proposal recently in the Journal of the American Medical Association (JAMA). Since then, the physicians have received some 6,000 letters about their plan. All were favorable.

The Medical Directive expands on, and remedies certain features of, so-called living wills, first approved in California 13 years ago and now legally endorsed in 75 percent of the states.

Living wills generally focus on opposition to having life prolonged by mechanical means if illness or injury occurs with no hope of recovery.

The Medical Directive, on the other hand, presents a series of theoretical situations, one or another of which is likely to apply in most circumstances involving incompetence:

- A coma with no known hope of regaining awareness,
- A coma with a small likelihood of recovering fully, a slightly larger likelihood of recovering with brain damage, and a much larger likelihood of dying,
- Irreversible brain damage or disease, accompanied by a terminal illness,
- And irreversible brain damage or disease which makes speaking or recognizing people impossible but which is not accompanied by terminal illness.

In each scenario, the person filling out the document indicates whether or not to designate interventions in any of 12 treatment categories. These range from resuscitation and ventilation to artificial feeding and simple diagnostic procedures.

In setting up the scenarios, the Emanuels included a clause advising that any treatment selected must be appropriate for the condition involved.

"That means a prospective patient cannot designate a kidney dialysis treatment, for example, if it would offer no help," Dr. Linda Emanuel pointed out.

She added that if a chosen treatment would clearly be futile, that is keep a patient alive but in a vegetative state, and the doctor is strongly opposed to such care, then there would be a genuine ethical disagreement between the two.

"A doctor and a patient should be able to discuss the dilemma and resolve their differences before the actual crisis comes," said the MGH physician. "When there is a disagreement that cannot be settled, even with the help of a medical ethicist, then I think the doctor involved is obliged to refer his patient to another colleague who agrees with the patient."

The Emanuels' plan allows for the designation of proxy decision makers, such as relatives or friends chosen by the patient.

"Such decision makers, however, do need a lot of advance guidance as to their decisions," said Dr. Linda Emanuel, who is also associated with Harvard Medical School's Division of Medical Ethics as Assistant Director in charge of program development.

"Proxy decision makers often don't know the patient's own views, and the proxy's ethical and psychological burden may prove overwhelming."

She cited a recently published study that further questioned the likelihood that proxy decision makers would decide for patients as the patients themselves would have decided.

In the study, investigators asked prospective patients whether they would want resuscitation or not. Then, the patients' wives and doctors were asked what they thought the patients' position would be.

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## *New Heart Aid*

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what interventions the device performed, and how the patient is doing.

Dr. Ruskin emphasized the importance of energy reduction whenever possible.

First, the energy actually required to do the job may be anywhere from a 30th to a 50th of what the original implantable defibrillator delivered. As a result, the shock experienced by the patient could in most instances be made much less painful and upsetting.

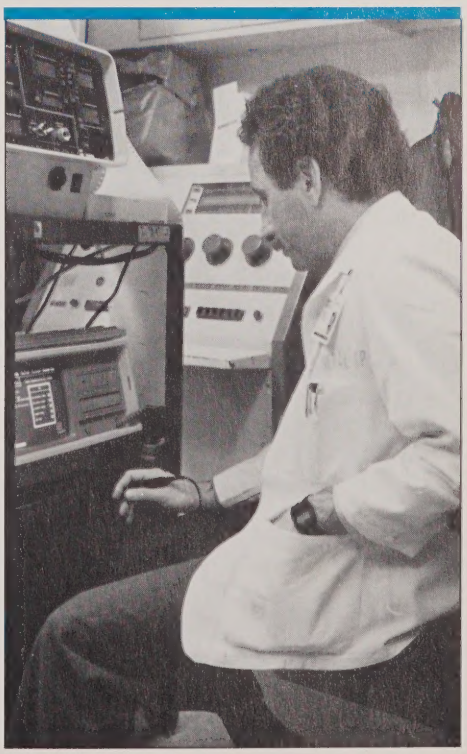
Second, the life of the lithium batteries that power the implanted device would be extended considerably.

"Although we don't yet know precisely how long the batteries will last," Dr. Ruskin said, "there is no question that they will last much longer than those in AICDs because of the increased versatility in Cadence and the fact that most of its interventions will involve tiny amounts of energy compared to the output of the high-energy device."

Experience has shown that an AICD can provide between 100 and 200 shocks before its pulse generator needs to be replaced. That usually means a battery life of about two years.

Currently Cadence costs more installed than AICD, about $18,000 versus $15,000, but because of the many tasks that Cadence can handle, Dr. Ruskin said he would not be surprised if standard defibrillators are no longer available in a couple of years.

"Devices like Cadence may be all that a physician will be able to get for a patient," he said. "When the batteries in the older version become depleted, the instrument may routinely be replaced with the more advanced equipment. A physician who wants to use the device just as a defibrillator can simply shut everything else off." ■



*Dr. Jeremy Ruskin studies computerized data showing how Leon Frank's heart is faring under the protection of his implanted multi-purpose assist device.*

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# Living Wills Can Be Misinterpreted

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"The spouses and the health care practitioners guessed very poorly," said the MGH physician. "Their opinions of the patients' medical care preferences were rated as little different than chance guesses."

In their JAMA article, the Emanuels wrote that "willingness to withdraw life-sustaining treatments decreases from 70 percent to 46 percent when the decision is not for oneself but rather for a relative."

Nine percent of Americans older than 18 have made out living wills, but although these documents have the endorsement of most medical and religious organizations, as well as many ethicists, the wills are seldom introduced in medical practice.

The reason offered by the Emanuels in their JAMA report is that living wills are "vague and difficult to apply."

"To many people, including physicians," the authors wrote, "living wills seem to be for the rejection of care — possibly even for accelerating death — rather than an opportunity for the patient to outline in advance a full range of preferences about medical care, including desires to have specific types of treatments administered."

Many living wills, they said, invite problems of interpretation. Most request cessation of life-sustaining care when "there is no reasonable expectation of ... recovery." Others direct physicians to forego "artificial means and heroic measures" or "life-prolonging procedures."

Some laws governing living wills also seem too inflexible, the Emanuels said, in that they may restrict these documents to terminally ill patients. Such living wills would not apply to patients suffering from no terminal disease process but still being sustained by medical technology.

Still another criticism of living wills cited by the MGH and Beth Israel investigators is that many are made out by people without consulting their physician. Instead, just as they would draft a will covering their estate, individuals who want living wills frequently go to an attorney and may confide in that person alone. In a crisis, a patient's doctor might not even know a living will exists.

Ever since the living will concept developed, a heated controversy has raged over whether the withdrawal of life-sustaining treatment includes artificially provided food and water. In other words, do such food and water constitute a medical intervention or simply basic care?

"I think the general consensus is beginning to be that food and water for someone who can't feed himself is a medical intervention," said Dr. Linda Emanuel, "but it's not an easy point. We include food and water in our Medical Directive as an intervention so that patients can give us a clear indication of what they think."

Commenting on the mail that followed the JAMA article describing The Medical Directive, she said that the first wave of letters generally came from MDs who had read the journal paper.

News reports generated a second wave of 1,000 letters a week, all of them requesting a copy of The Medical Directive. More than 20 percent of these writers were attorneys who wanted the document for their clients. The continuing demand for the Directive has forced the Emanuels to send it only to those who supply self-addressed return envelopes, and even that fails to cover costs.

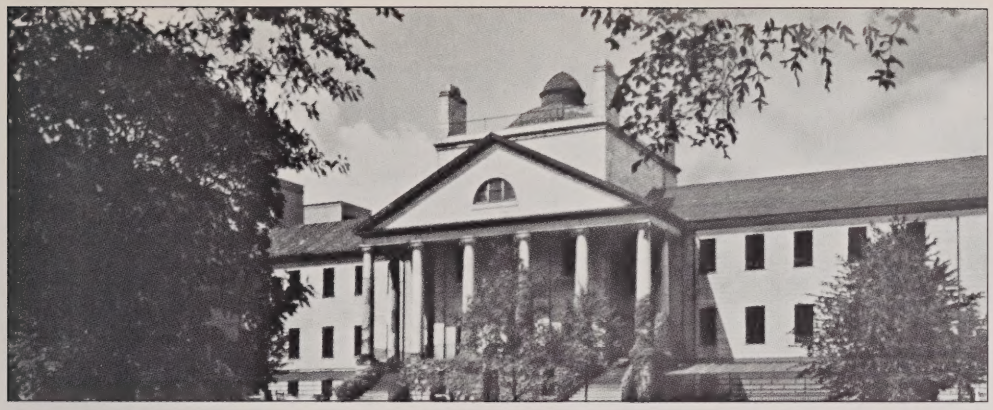
With funding from the National Center for Health Service Research, a branch of the National Institutes of Health, the Emanuels and two other physicians from the MGH, Drs. John D. Stoeckle and Michael Barry, are presently studying how The Medical Directive fares when used.

"We've interviewed 500 patients who have completed a Medical Directive with us," said Dr. Linda Emanuel, "and are following them over time to see whether they change their mind, either before or after they get into medical trouble.

"Also, we want to see whether people make a lot of inconsistent selections, which would allow us to fine tune the Directive. We might need to change some scenarios or drop or add a couple of interventions."

Drs. Linda and Ezekiel Emanuel hope that soon they will be able to arrange multi-centered trials to obtain an even broader assessment of the contribution being made by The Medical Directive. ■

*Dr. Linda Emanuel reads some of the thousands of letters she received following a scientific journal report on The Medical Directive which she and her husband, Dr. Ezekiel Emanuel, devised as an improvement on living wills.*



Massachusetts General Hospital, Boston, Massachusetts

MGH News

Vol. 49 No. 2 March 1990

# Transplant Needs Spur Hopeful Studies

IN LATE 1984, much of the nation's attention was riveted on a battle to save an infant's life in a California hospital.

Baby Fae had been born with a fatally defective heart, and at 11 days of age, in a desperate attempt to keep her alive, surgeons replaced her heart with that of a 7-month-old baboon.

As the nation followed daily news accounts about Baby Fae, her body rejected the baboon heart but not until she had lived with it for three weeks. No other human recipient of an animal heart had survived longer.

Xenogeneic transplantation, the transplanting of organs or tissues from a member of one species to that of another, has been attempted some 30 times in humans since 1960. Kidneys, livers, and hearts have all been used, but only from primate sources.

None of the transplants survived for a full year, but one patient did live for nine months with the kidney of a chimpanzee. The patient succumbed from an infection without evidence of the donated kidney being rejected.

Although xenografts have not been successful on a long-term basis, they have taught researchers that nonhuman organs can support human life, even with less advanced methods of preventing graft rejection than are available today.

With the increasing success of allogeneic transplantations — the transfer of organs or tissues between humans — a relative shortage of human donor organs, such as the heart, kidney, and liver, has developed. This has renewed interest in the possibility of using organs from other species to benefit humans.

*In the MGH Transplantation Unit, a team headed by Dr. Hugh Auchincloss, Jr., has found indications that xenografts may in some respects be better organs to transplant than allografts.*

One must first understand that the human immune system has two ways to fend off alien organisms.

One way is for the foreign tissue to be

*(Continued on Page 4)*

# Exposure to Language Begins Before Birth

MOST PEOPLE regard birth as the beginning of experience. Actually, it is not.

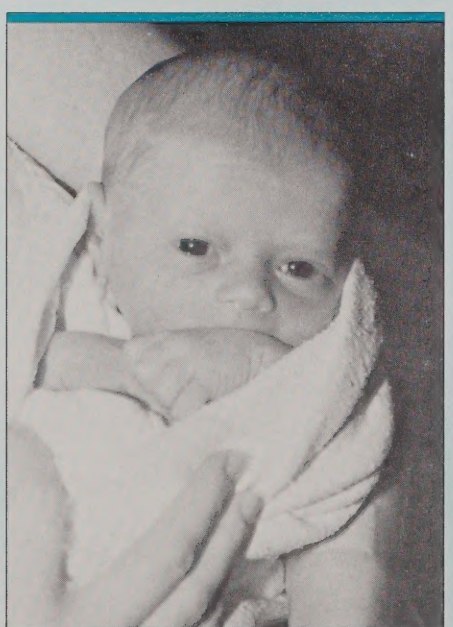
Even as it lies in its mother's womb, a fetus is often exposed to patterns of stimulation relevant to language and reacts in developmentally favorable ways.

"There is pretty solid evidence that vocal learning precedes birth," said John L. Locke, Ph.D., Director of the Neurolinguistics Laboratory at the MGH and Professor of Speech-Language Pathology in its Institute of Health Professions. "We believe, for instance, that a fetus can hear after only 24 weeks of gestation."

Imagine the face of a fetus conveyed to a video screen by ultrasound techniques and then the introduction of sound near the maternal abdomen. Whenever the tone is presented, the fetus will be seen blinking.

A hydrophone, used to record underwater sounds, has repeatedly detected a

*(Continued on Page 2)*



*Only two days old, Allison Daniels of Baltimore waits to learn more about her new world.*

# *Overcoming Feelings Of Guilt and Shame From Child Abuse*

MANY child victims of incest who have grown to adulthood hiding their psychological pain are finally beginning to speak out.

An MGH program that the hospital's Social Service Department calls Women Helping Women is providing an environment in which adult survivors of incest can work together to deal with feelings of guilt and inadequacy that have haunted them for years. Even male partners of these women have their own group therapy to help them cope with problems related to the incest.

Surveys indicate that at least five percent of all women were sexually molested as children by family members, most often a father or stepfather. Frequently sexual abuse begins when a child is very young. It can range from one episode to abuse that continues for many years.

In the past, children have been discouraged from telling of sexual abuse because to do so threatened destruction of their family. Taught to regard their parents as good and protective, children often did not recognize the parents' behavior as improper. Yet, the youngsters felt instinctively

*(Continued on Page 5)*

## INSIDE:

**Page 7**—Head injuries sometimes defy detection.

EDITORIAL

# The Miracle of Life

The miracle of life: The fetus in its wet, close, dark, invisible world, hears. Not only hears, but apparently learns to distinguish the mother's voice. Not only distinguishes her voice but also seems to recognize the patterns of the language she speaks.

Then the miracle of birth. The helpless infant is thrust into a room that by comparison is colossal. Surrounded by light and sounds, some from machines, others from living beings... These strange humans admire the babe. They talk to it as though this newborn can understand. What a bewildering little world — one created, it seems, to entertain the infant. Certainly these few pounds of flesh are the center of its own universe. By crying and laughing, it commands the actors who share its stage to follow its bidding.

What a grand little world. By degrees, though, that world enlarges. From a room to a house. To outdoors. To an automobile. Maybe even an airplane, a thundering monster which creates sickening sensations of movement; of pressures which torment the ears. Now that voyage which began in the tiny, dark chamber inside the mother has exploded. Out there is the cosmos, an unthinkable, infinite expanse. No longer is that once infant the center of even its own universe. That lesson is one that comes hard. Secretly — maybe not so secretly — we all venture but a few toddling steps from the small room of our birth. We find it difficult to really escape the universe with ourselves as its center. That is why Galileo was not believed. It is too wrenching to conceive of a world in which we ourselves are not the central players.

## *Learning to Speak*

*(Continued from Page 1)*

mother's voice in the fluid-filled sac carrying her fetus. The voice appears reasonably intense at the ear of the unborn infant. While it is not known how much information the fetus actually acquires in utero, there are two effects at birth which suggest that it indeed learned something about the mother's voice.

Researchers have found that if a baby is exposed during its first three days of life to two speakers, one carrying its mother's voice and the other someone else's voice, the baby will turn toward the sound of the mother presumably because it has heard that sound before.

The second effect, discovered by investigators in Paris, is that a baby prefers to hear someone speaking the same language as that of its mother. A baby born to a French woman, for instance, would become more aroused by the sounds of French than the sounds of other languages. Differences in rhythmic aspects of the languages apparently enable the infant to differentiate.

"Spoken language is a part of every human culture; in none is there only sign language," Dr. Locke pointed out. "Exposed to varied sound patterns during the fetal stage of development, babies seem to enter the external world with their brain already primed to learn how to process sounds."

Unless a child is brain damaged, deaf, or emotionally disturbed, it does not have to be taught how to speak. The child will develop speech on its own, and because this occurs so naturally, people do not really consider the learning process that is involved.

"Parents unwittingly play a far more ac-

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PHOTOGRAPHS: Page 1, Robert Daniels; page 3, Kennetha Bigham; all others, Myron Daniels.

tive role than they think in inducing their children to pay attention to vocal patterns," said Dr. Locke. "In the process of making speech interesting, they are probably increasing their children's capacity to learn speech and to process speech as produced by others."

Upon birth, babies are exposed to human faces before anything else. The faces move and with the movements come voices, sounds like the sounds the infants heard before.

As early as the first hour of life, babies can detect facial expressions well enough to imitate them. A smile, an open mouth, a tongue sticking out of the mouth, all may induce the baby to respond in kind.

Babies are especially aware early on of a parent's eyes. If a mother, for instance, is cooing to her infant in an attempt to induce vocalization but is wearing reflective sun glasses that hide eye movements, the baby would be less inclined to be vocal.

A face that is smiling is more likely to elicit sounds from a baby than a face that is not smiling. And for some unexplained reason, a smile that shows the teeth is more evocative than a smile that does not.

"If a mother who is normally responsive to her baby is instructed to look at the infant with a poker face," Dr. Locke said, "the baby will turn away from the face, then seem to look back at it, almost to note if the facial appearance has changed, then look away again. The baby will likely become agitated and restless."

After a minute or two, the mothers usually ask to be relieved of their poker-face role. They find acting out the part to be emotionally difficult.

A precondition for learning language is "turn taking." This begins with feeding episodes during the first several weeks of life.

"I think it actually begins with oral sucking patterns by the newborns," said Dr. Locke. "They suck in bursts, pressing their tongue against the nipple five, six, or seven times in a series. Then they relax for five to 10 seconds. This pause, whether it be during breast feeding or bottle feeding, enables the mothers to inject their own behavior."

During the pause, the mothers characteristically jiggle the baby or the bottle to try to induce a resumption of sucking. The mothers soon realize that too much shaking only delays the continuation of feeding. They adapt. In time, both they and the babies learn when to "take" the floor and when to "yield" it.

In their earliest interactions, the parent and the baby tend to vocalize at the same time, to interrupt each other. In retarded babies, such as those with Down's syndrome, this vocal clashing tends to continue throughout their first year. But in the normally developing infant, clashing usually diminishes when the baby is around 12 to 18 weeks of age, when the parties begin to alternately "take" and "yield" the floor. Dr. Locke considers this vocal turn-taking a necessary condition for efficient language learning.

In encouraging an infant to vocalize, Dr. Locke said, it is important to let the baby fully emit the sounds it wants to make. Even though these sounds may make no sense, they should then be incorporated into adult responses.

For instance, if the baby says "ba" and the mother repeats "ba," the baby is likely to say "ba" a second time. A basis is thereby being created for the parent and infant to do something together, a framework for vocal learning which builds upon the babbling that normally begins between six and 10 months of age (*MGH News*, January-February 1985).

Soon after babbling begins, babies also learn to point. If a baby points to a ball but can only utter "ba," the mother can fill out the word. "You want the ball? Yes, that's a ball. Let's get the ball. It's a big ball, isn't it." The baby may now say, "big ball."

*Dr. John Locke and Research Associate Dawn Pearson analyze a sound spectrogram of a baby's developing speech.*

Dr. Locke, who is also on the faculties of Harvard Medical School and M.I.T., cautioned that during vocal learning babies find that speech has a special value. They discover that they can express feelings of discomfort, fatigue, irritability, and even of joy by simply unleashing vocal outbursts. Their voice, they find, is an instrument by which parents can be summoned quickly to provide various kinds of accommodations.

In a book that Dr. Locke is writing, entitled "Development and Application of the Capacity for Spoken Language," he underscores his belief that a baby is a key player in the development of its brain.

People, he said, think of language in a biological framework, implying that "genes give you a brain and the brain gives you behavior. I think that is misleading. A baby's brain initially has some structure that causes limited amounts of behavior. The brain then responds to the behavior that the baby produces, and the other stimulation it receives, and grows accordingly, increasing the capacity for more behavior."

Babies have a keen appetite for certain kinds of experiences, the MGH neuropsychologist explained. They want to listen to certain sounds, to make specific movements, to touch a variety of objects. These desires, he said, create a backflow to the brain, and the parts of the brain genetically programmed to perform certain functions are thereby activated.

"Not only is an infant an exceedingly active agent in the development of its own brain," Dr. Locke said, "but similarly its parents are exceedingly active agents in the development of the social basis for language development." ■

# *Special Antibody Helps Research Grafts*

*(Continued from Page 1)*
attacked by T lymphocytes (white blood cells that form in the thymus gland). This is called cellular immunity.

The other method is for B cells (believed to develop in the bone marrow) to produce antibodies which then attach to the foreign tissue. The B-cell antibody action is also called humoral immunity.

Studies have demonstrated that the immune response to xenografts very strongly involves the B-cell or humoral immunity.

"We think the liver is particularly resistant to antibody-mediated rejection," Dr. Auchincloss said. "We also believe that under certain circumstances pancreatic islets, which are the source of insulin, will resist this type of immunity. *In view of these indications, we may be able to use xenogeneic sources of those tissues for transplantation in the future."*

*It has been thought that the more disparate a species is from humans, the stronger the T-cell immune response will be. "This doesn't appear to be so," Dr. Auchincloss said. "We believe that the more different the graft is, the more xenogeneic it becomes, and the cellular immune response actually seems to become weaker in some respects."*

Dr. Auchincloss said that Baby Fae received very high doses of immunosuppressive drugs to knock out the T-cell response to her baboon heart, but despite those drugs the xenograft was rejected by the B-cell immunity.

"While we have very good drugs to deal with T-cell immunity, such as cyclosporine, steroids, and OKT-3 (a target-specific, monoclonal antibody developed at the MGH), we're still experimenting with ways to block B-cell immunity," he said.

Two new antirejection agents called FK506 and 15-Deoxyspergualin, currently available only for research use, have prolonged xenograft survival but are more effective on allografts.

"They don't seem to be the magic bullet that's going to clear the way for xenografting," Dr. Auchincloss commented. *"With one exception, it always seems to be harder to make the xenografts survive than the allografts."*

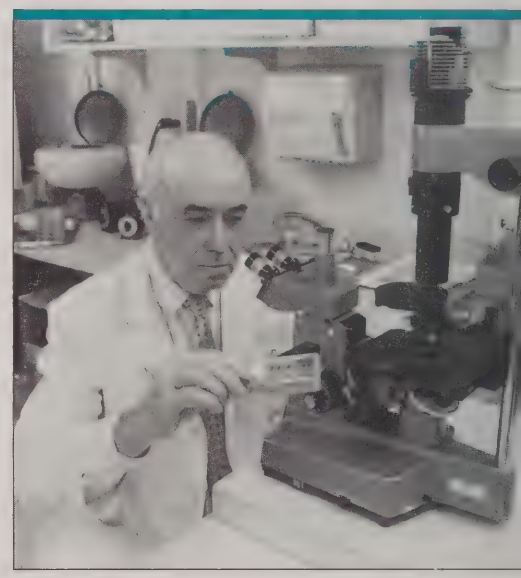
*That one exception, he said, involves a monoclonal antibody directed against a subset of T cells called CD4. In MGH mice experiments involving this population of cells, the anti-CD4 antibody prolonged the survival of skin xenografts from rabbits and monkeys without extending the survival of allografts from other mice, a remarkable result.*

The work was reported in the *Journal of Experimental Medicine* by Dr. Richard N. Pierson III, Henry J. Winn, Ph.D.; Dr. Paul S. Russell, and Dr. Auchincloss.

Recently, MGH investigators transplanted pancreatic islets from sheep into diabetic monkeys. So far there has not been any dramatic reversal of the diabetes, but the work is only in its early stages.

In the past, rat islets have kept a monkey's blood sugar relatively close to normal for a short period. Human pancreatic islets also have been used successfully in mice to regulate their blood sugar. And insulin from pigs or cows is often used successfully to treat diabetics at present.

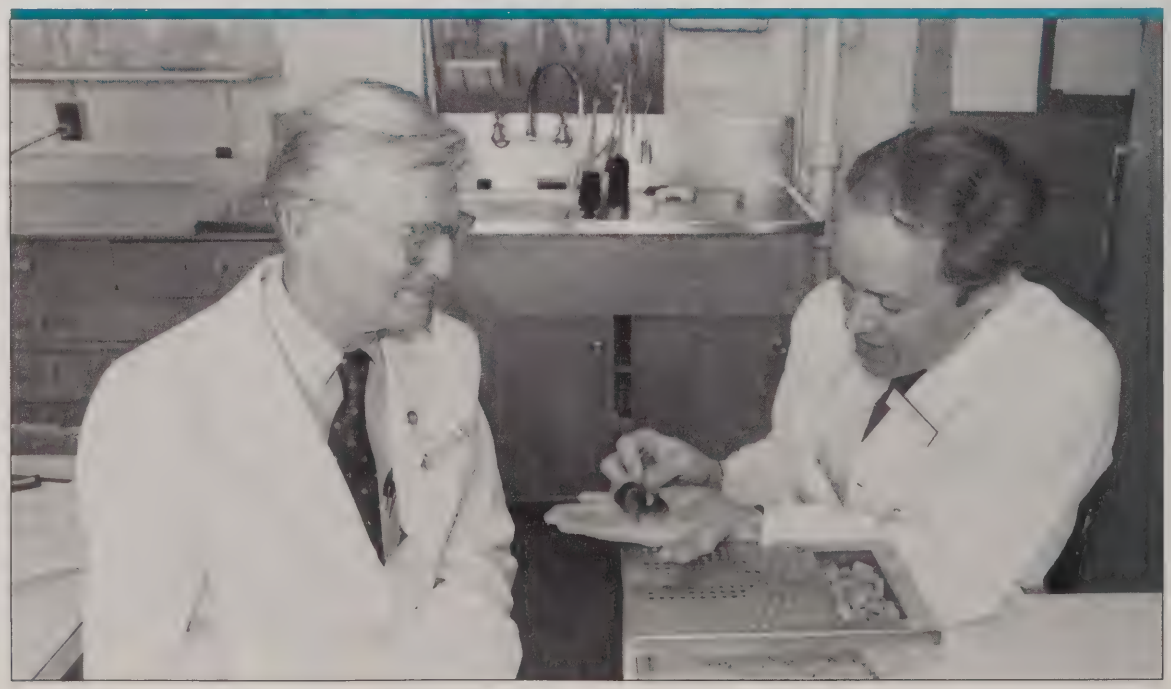
Dr. Auchincloss, who is also a general surgeon at the MGH, expressed doubt that



*Dr. Henry Winn studies the effects of monoclonal antibodies in determining what mouse T cells would kill rat target cells.*

using primate grafts for humans will be the way of the future.

He offered two reasons. First, not enough chimpanzees or baboons are available in this country for such a purpose. In a given year, for instance, only about 60 chimps can be obtained for research work in the United States. The supply is small because



*In the Transplantation Unit, Drs. Paul Russell, left, and Hugh Auchincloss, Jr., inspect a mouse that is about to receive a small skin graft from a monkey.*

primates do not breed well in captivity.

Then, as evidenced by the Baby Fae episode, whenever a primate is mentioned as an organ donor for a human many people become very uncomfortable. A baby primate in a person's arms can appear to have very humanlike qualities.

"We need to move further away from humans to find our donor source," Dr. Auchincloss said. "We're focusing more on pigs. Their organs are about the right size. Pigs breed very quickly, produce large litters, and have long provided food and other support for humans."

Countless people stricken with a faulty valve in the heart, including the late John Wayne, had material from pigs serve as valve replacements. The pig valves are not live tissue but have just the right configuration to act as a valve. And they fulfill a key human need.

It is not known how well a functioning organ from an animal other than a chimp or a baboon would survive in a human. But as far back as the 1960s some human patients suffering from acute liver failure were kept alive by filtering their blood through a pig liver and then returning the blood to the patient. The pig livers functioned so well that the patients improved.

Dr. Auchincloss, who is also Assistant Professor of Surgery at Harvard Medical School, said that the use of a pig liver to replace a child's own failed liver may be a real possibility within the next decade.

*"Getting livers for children is particularly difficult," he said. "That's why one hears today of efforts to pare down the liver of a surviving adult relative to create a transplant for a child. There just aren't enough donor livers for youngsters."*

He also expects to see the transplantation of pancreatic islets from animals to humans in the coming decade.

"If we could start treating diabetes with islet cells, the number of people who could benefit would be huge," he said. "We would need a new source of tissue which might come from sheep or pigs, some distant species of moderately good size."

The islets would be placed in the patient's portal vein which extends from the bowel up into the liver. There would be no need to interfere with the patient's pancreas whose insulin production has failed.

Dr. Auchincloss said that one might consider breeding a colony of pigs as perfect donors for humans. Selected for their weak capacity to elicit a human immune response, the pigs would be bred without any diseases that could affect humans. In addition, techniques available in molecular biology could be applied to prevent certain genes from being expressed in pigs that might otherwise increase the danger of graft rejection

Dr. Auchincloss believes that breeding such a colony of pigs could begin in just a couple of years. ■

# *Incest Victims Absorb Responsibility*

*(Continued from Page 1)*

that something was not right, and they absorbed responsibility for it.

In the years that followed the incest they found themselves plagued by chronic guilt, shame, loneliness, and vulnerability to repeated exploitation.

The secrecy that perpetuated these unbearable feelings began to wane a few years ago when people started inquiring about the existence of therapy programs for adult incest survivors.

What created the momentum for these inquiries is uncertain. The women's equal rights movement encouraged women to speak out. In general, however, the adult survivors may have felt that today's society had become more responsive in dealing with such delicate subjects as incest and its consequences.

At the MGH, the inquiries about group therapy reached Deborah Hill, director of a Social Service program that assessed and treated child abuse and neglect.

Ms. Hill realized that no group therapy programs existed at the MGH for adult victims of childhood incest and immediately set about starting them.

In collaboration with Ruth Paris of the Social Service Department, Ms. Hill five years ago organized and led three 12-week groups a year. They were so successful that waiting lists for enrollment quickly developed. One year ago, under the title of Women Helping Women, the program was formally expanded.

There are now two 12-week therapy groups, one codirected by Alice Curnin and Amy Davis, the other by Donna Miller, and a 20-week group, conducted by Susan Primm and Christine Bowling.

Another therapist, Susan Chauncey, directs a 12-week program that began for the male partners of female incest survivors. And Margie Magraw and Andra Adams run a 12-week program for adults raised in families in which one or both parents suffered from alcoholism, drug use, manic depression, or severe emotional problems.

All of the therapists who staff Women Helping Women are licensed social workers with master's degrees.

Ms. Hill said that in her 25 years with the MGH, including its health center in Chelsea, she has never found working with any single population to be as rewarding as her association with the women incest survivors because of the courage and commitment that they demonstrate.

"They come and share incredibly painful and heartfelt feelings," she said, "and take great risks in doing so because their history certainly hasn't given them good reason to be trusting.

"Coming with very diverse backgrounds, they are pulled together in the very first session by the commonality of their experience, namely the incest. The women work together in a way whereby they empower each other to achieve their goals. When the women come out of the group, they are usually very different people than when they went in."

Candidates for the adult incest survivor groups, which are limited to eight members each, are screened with extreme care. Each

*(Concluded on Page 6)*

*Deborah Hill of Social Service conducts a group meeting.*

# *Members of Groups For Incest Therapy Are Carefully Chosen*

*(Concluded from page 5)*

prospective member is already undergoing individual therapy. Although group work is a central part of the Women Helping Women program, individual therapy is also available within the program.

Alice Curnin said that after many years of concealing the incest, breaking the silence is often done gradually. Is the group candidate, who may have told only her individual therapist, ready to share the secret with others?

The timing is important, Ms. Curnin stressed, because listening to the stories of others in the group can trigger a release of long-suppressed memories. "It can be a flooding of very intense feelings," she said.

Many of the women are in important relationships, and some have children of their own. Unwanted memories may return in a variety of circumstances. One example is when a child reaches the age when her mother was victimized.

The aim of the group therapy is to integrate the incest experience into the women's lives in such a way as to have less of a hold. While the incest can never be erased, the therapy can help the women gain greater control of their lives.

Ms. Curnin said that "it is important for women to realize that incest is not about sex but about an abuse of power."

When a woman tells her story within a group, others may quickly say, "It wasn't your fault." Forgiving oneself takes longer. However, much progress toward this is made in group sessions.

Having an intimate relationship revolving around trust, closeness, and mutual dependency is often much harder for a woman who experienced incest as a child. Lack of intimacy frequently leaves the male partner feeling rejected or abandoned.

Susan Chauncey, who conducts group therapy for such male partners, said a woman may truly love her husband but memories of her childhood abuse may be stirred at times of physical contact and the woman may wonder whether her partner is her husband or the abuser.

The frustrations that the couple experience are not caused intentionally by either member, Ms. Chauncey said, but to protect herself the wife may find it necessary to erect walls. Sometimes she is also concerned about the family's children out of fear that what happened to her might befall them as well.

In screening prospective members for her group, Ms. Chauncey makes sure that those who are enrolled have some similar difficulties. Interaction among the members to help settle issues is facilitated if the discussions involve mutual concerns.

Often the men come to the group sessions not only seeking ways of coping with their wives' behavior but also wondering whether something in their own background contributed to the marital dilemma. Were the husband's own parents less nurturing than they might have been?

By sharing experiences and hearing suggestions from others, each man is helped in deciding how best to resolve his own situation and still maintain a closeness with his mate.

What is it like to be reared by parents who suffered severe problems? At group meetings conducted by Margie Magraw and Andra Adams, adults raised in dysfunctional families discuss the impact that the adverse conditions had on them.

Again, through careful screening, the group members have a commonality that encourages interaction. But unlike the other groups sponsored by Women Helping Women, the therapy is predicated to a large degree on role playing. The social workers call it psychodrama.

Suppose a woman, let's call her Kathy, complains of a raging argument with her boss over an office assignment. She was particularly disturbed because the dispute felt so familiar. Instead of trying to describe what happened, Kathy picks someone in the room to play her boss and they act out the event.

Ms. Magraw or Ms. Adams might stop the play acting and ask Kathy, "Where have you felt this before?" The response might be, "Oh, I felt this a million times before with my mother. Once I fell into a lake, and my mother's reaction was to accuse me of being clumsy."

The acting resumes, this time with Kathy playing the mother as the mother was and later as she wished the mother had been. As a result of the role playing, Kathy may begin to see that her boss was not her mother and/or that the boss had asked, not demanded, that she do something. She may now realize that her reaction to the boss was inappropriate or that there might be other ways to react.

"When we ask our clients to play roles, we're really asking them to recognize their own feelings," Ms. Magraw said. "Because of the common feelings that these issues produce, it's almost impossible for a member to act out a role without it tapping into the issues and feelings of other group members.

"Our group has clearly affected people's lives. We don't purport to change their lives, but we try to open doors for them that they haven't had access through before. A group also gives one the reality of being part of a community, and that brings a new sense of being able to cope."

Deborah Hill said that women seeking to join therapy groups conducted by Women Helping Women are initially anxious at interviews.

"They're frightened because what they have to tell is so painful," Ms. Hill said. "I want to assure them that all of the women applicants feel that kind of anxiety. It will pass. The women generally feel much better after the interview, which doesn't commit them to anything." ■

*Alice Curnin, left, and Margie Magraw of Social Service discuss an applicant's request to join a Women Helping Women therapy group.*

*Applicants for group therapy conducted by Women Helping Women can make appointments for an interview by calling the program's secretary, Ms. Eileen White, at (617) 726-2623 between 8:30 am and 5:00 pm on weekdays.*

# Head Injuries Sometimes Defy Detection

EACH YEAR, an estimated 1.5 million Americans suffer head injuries in accidents, and much is written about how modern technology saves many from infirmity or death.

Motor vehicle accidents account for most head injuries. Falls rank next. Then there are miscellaneous mishaps, e.g., somebody is whacked on the head by a baseball or a bat, a suitcase falls from an overhead storage rack on a plane or train and hits a passenger, a person rises too quickly from a chair and his head strikes the bottom of an open cabinet door.

The spotlight focuses on the seriously injured, such as those suffering skull fractures, bleeding in the head, a swelling of brain tissue, or cranial nerve damage.

But what of the rest of the head-injured population who seek medical attention. On the basis of negative findings in neurological tests, 70 percent of people who suffer head trauma in accidents each year are judged to be only mildly affected. Yet, after weeks have passed, as many as half of these individuals will insist that they feel anything but recovered.

Despite the lack of documented evidence, they complain of a great variety of ills. Headaches that do not seem to get better lead the list. Other effects include dizzy spells, amnesia, blurred vision, ringing in the ears, insomnia, difficulty concentrating for more than a few minutes, and inability to process information with the same speed as before.

In years past, many people who complained of head trauma but lacked evidence of it were perceived as malingerers or as predisposed to psychological disorders.

The advent of computer technology has helped to dispel these notions. By tracking the progress of thousands of patients with mild head injuries, computers produced convincing evidence that the symptoms these people complained about were real.

Some patients might rightfully be classified as malingerers, it was thought, but how could thousands be. As for whether mild head trauma has a mainly psychological or physical basis, most physicians today believe that the damage is probably physical, microscopic, and diffuse throughout the brain.

Brain fibers might not be torn as in a severe injury, but they might have been stretched badly, causing functional disturbances just as significant.

Even though a head trauma patient's neurologic exams may prove normal, the attending physician, usually a neurosurgeon in a hospital Emergency Room, strives to learn from the patient (and, if possible, from a witness) whether loss of consciousness had occurred.

Injured in an auto collision, for instance, a patient is asked what he first remembered after the accident. "I found myself lying in the ambulance," he might say. Or, "the doctor was examining me here in the Emergency Room." That reveals anterograde amnesia.

Some people will recall events that occurred right up to the moment of a crash. Others may not even remember why they had left their house. The latter is retrograde amnesia.

Unconsciousness lasting less than 20 minutes could indicate a shaking or jarring of the brain (a concussion) or, if longer, a bruising of the brain (a contusion). CT (computed tomography) and MRI (magnetic resonance imaging) studies are both very useful in producing more definitive diagnostic assessments.

Dr. Charles E. Poletti, an MGH neurosurgeon, emphasized that an accident victim can develop memory lapses without ever losing consciousness. And because he did not pass out in the mishap, the victim may tend to minimize the seriousness of a head injury and regard a medical evaluation as unnecessary.

"Although mild head trauma will resolve in most instances as time passes," Dr. Poletti said, "there is a large group of people who are mistaken in thinking that the injury is mild.

"People can even have an intracerebral hematoma (a collection of blood in the brain) and never realize it. Alterations in very sophisticated higher levels of intellectual function might develop in their work performance one, two, even three years later without being ascribed to the accident."

The head need not strike an object for an injury to occur. Dr. Poletti said that whiplash, the snapping backward and forward of the head in motor vehicle collisions, commonly leads to mild head trauma (*MGH News*, December 1989).

A Pain Research Laboratory, directed by Dr. Poletti in the MGH Neuroscience Center in Charlestown, is trying to assess the role that nerves in the upper cervical spine, or neck area, play in head trauma.

Even if CT, MRI, or an assessment of the brain's thinking processes (corticol function testing) fail to spot the root of

*(Concluded on Page 8)*

*Dr. Robert Hartley of Sherborn, MA, who suffered a head injury in a recent automobile collision, performs a balancing exercise supervised by Dr. Elaine Woo at the MGH-affiliated Spaulding Rehabilitation Hospital.*

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# *Mild Head Trauma Often Lacks Proof*

(Concluded from Page 7)

mild head trauma, Dr. Poletti said a number of studies have emphasized the importance of rest to overcome the syndrome (group of symptoms) of headaches, dizziness, decreased ability to concentrate, etc.

"The evidence is fairly strong," he said, "that people who immediately go back to stressing their systems tend to prolong their illness. Studies have recommended two to six weeks of rest. This would seem to substantiate the view that the syndrome is based on an altered functioning of a normal nervous system rather than on some psychological phenomena."

At the MGH-affiliated Spaulding Rehabilitation Hospital in Boston, Dr. Elaine Woo directs a 19-bed Adult Head Injury Unit which treats about 120 patients a year.

Some are referred to her unit one or two weeks after being treated and stabilized in an intensive care unit at the nearby MGH. In other instances, patients are referred to Dr. Woo's group long after an accident because of a perception that a condition has suddenly worsened.

Dr. Woo is particularly interested in patients with mild head trauma because in a sense she regards them to be a disenfranchised population. Inasmuch as they present no clear-cut proof of illness, their complaints often fall on deaf ears. At the same time, spouses demand to know, "What is the matter with you?" and employers warn, "Your work has been falling behind. You'd better shape up." Such remarks only fuel frustrations.

"The whole point of our rehabilitation program," Dr. Woo said, "is to help other parts of the brain compensate for a lost skill. We try to teach people how to get around an acquired deficit."

Of all the traumatic effects of a head injury, among the most devastating, she said, are disturbances of cognitive and intellectual functioning. Areas of the brain commonly disordered deal with planning, behavior (such as control of one's emotions), initiative, and mental capacity (not only how much one can do within a certain time but also how quickly one can perform).

Getting the mild head trauma patient on the road to recovery is accelerated by making not only the patient but also family members and employers understand just what deficits the accident had caused.

During one to two weeks of hospitalization at Spaulding, patients undergo a battery of special customized tests

*Mirrors help accident victim Robert Hartley evaluate his progress in therapy to help him regain normal balance.*

designed to create a blueprint of what happened to them. When they leave the hospital they carry recommendations of compensatory measures.

These might include writing things down to jog the memory, making the daily activities schedule more routine, breaking work loads into smaller chunks that require less concentration, and resting periodically to regain endurance.

Underlining the importance of support and encouragement from relatives, close friends, and employers, Dr. Woo remarked:

"A cast on a broken leg carries an important message. The cast says to the patient and those around him, 'I have an injury. Give me a hand. Hold the doors for me. Don't make me walk through endless slush from the parking lot.' With head injuries, a patient still needs a helping hand but because he doesn't wear any kind of cast he can't always 'access' the much needed support and encouragement."

After their hospitalization at Spaulding, head trauma patients are further assisted there on an ambulatory care basis. Patients may wish to visit two or three times a week for help with speech or for occupational or physical therapy. Or they may simply want to consult with a member of Dr. Woo's staff on how they are progressing.

The average treatment program, including the outpatient phase, could last a few months, but as Dr. Woo put it, "In the meantime, life has begun again for these patients. They're not crippled or on the back burner." ■

## In Doubt? Check It Out

Not everyone who bumps his head in an accident needs medical care, but the individual should be monitored closely for any change in mental or physical functioning, such as decreased alertness, lapses in memory, a shift in speech patterns or behavior, or weakening of a limb.

In short, said Dr. Charles Poletti, an MGH neurosurgeon: "Anybody who gets worse instead of better should seek an immediate medical evaluation."

Ideally, the patient should be seen in a hospital Emergency Room by a specialist in neurological disorders who can conduct or order appropriate tests.

If the patient lives in a small town lacking a hospital, a family practitioner who has known the patient for years would be in a good position to make an evaluation.

MGH News

Massachusetts General Hospital, Boston, Massachusetts Vol. 49 No. 3 April 1990

# Trying to Overcome Low Back Pain and Sciatica

IMAGINE being unable to sit, stand, or walk because of unbearable pain, and of being afraid to cough or sneeze lest the pain increase.

Nerve pain ranks among the most severe physical distresses that humans endure, and of all the nerves that incapacitate, none has a more widespread effect than the longest nerve in the body, the sciatic nerve.

Beginning in the buttocks, the sciatic nerve runs down the back of each thigh to the knee, then breaks into two branches, the posterior tibial and peroneal nerves, which extend farther down each leg.

Although the sciatic nerve is subject to a variety of disorders, such as direct injury, infections, and tumors, the pain that radiates through it and its branches stems 98 percent of the time from compression of one of its roots in the lower (lumbosacral) region of the spine.

The pressure may come from rupture of a cushioning disk between two vertebrae or from a bone spur caused by osteoarthritis, a degenerative joint disease.

The sciatic nerve originates from two primary roots. One emerges above the fifth lumbar vertebra, the other above the first sacral vertebra. They meet in the pelvis, in a network of nerves called the lumbosacral plexus, to form the sciatic nerve.

More than five million Americans suffer from disabling low back pain, but *(Continued on Page 2)*

# *A Magnetic Stimulator May Help Uncover Nerve Diseases*

A DEVICE that magnetically stimulates a command post in the brain is being studied for possible use in helping to diagnose major diseases of the central nervous system.

In the past, efforts to identify such conditions as multiple sclerosis, amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease), and spinal cord injuries have been hampered by the absence of a major piece of information in the diagnostic puzzle.

"We have known for many years how to evaluate both sensory and motor nerves in the peripheral nervous system, such as in the arms and legs, because those nerves are accessible to us," said Dr. Keith H. Chiappa, Director of the EEG (electroencephalograph) Laboratory at the MGH. "By simply putting a harmless electrode over a peripheral nerve and stimulating it with an electrical pulse, we can then see how well the nerve performs.

"Up to now, however, neurologists have had no objective way of checking the function of the motor system in the brain and spinal cord without participation of the patient."

To judge this motor function, or how well the brain's commands to muscles are reaching the muscles, a neurologist might instruct a patient, "Tighten your biceps and don't let me pull away from you." Or the physician might put his fingers in one of the patient's hands and say, "Squeeze my fingers as hard as you can."

Whatever the test, its outcome hinges on how well the patient cooperates. Sometimes inability to understand what is going on or being in a coma makes coop- *(Continued on Page 6)*

## INSIDE:

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**Page 7** — Hiccups: As many causes as treatments

EDITORIAL

# Change for the Sake of Change ...

The Food and Drug Administration (FDA) has long served as a defender of the American public, protecting people from charlatans and overzealous profiteers. It was not that many years ago that less than honest businesses could advertise a "medication" which "cures" a score of ills. In many foreign nations that practice remains unfettered with serious consequences for the health of the inhabitants.

Indeed the FDA tends to be more strict than similar government agencies in Europe. Many, perhaps most, times that conservatism seems to work to the advantage of Americans who in one dramatic, often-cited instance were spared the thalidomide disaster which crippled so many European newborns whose mothers took the drug during pregnancy. Often, though, the FDA process seems cumbersome. People often complain that it takes too long — sometimes much too long — to approve a drug which is clearly beneficial.

Many opponents of the FDA have been far from shy about their hostility. Until now, however, the governmental agency has been impervious to major change. Often alterations in procedures of a large organization change only when conditions change. In this instance the catalyst is AIDS. Other diseases such as cancer also cause fear. Some like an influenza epidemic have swept through the population quickly and lethally. In this century, AIDS comes to mind as the only epidemic with all these attributes: 1. It came without warning and for a while was an enigma. 2. It spread at an incredible rate. 3. It seems to be universally fatal. For any disease to have only the last element is frightening enough. To combine all three characteristics can be terrifying.

For a while many people consoled themselves with the belief that they were safe because they were not in a high risk group. Now even that thought offers less consolation. It is thus no surprise that patients afflicted with AIDS have commanded attention for their demand to receive drugs which may be promising. A few of these medications have had some beneficial effect. Many have been worthless and others harmful. There is no question, however, but what people with AIDS have managed to dramatize their urgency for quicker and universal access to unproven drugs. The FDA has been listening and acting. Even more important for the FDA's long-range mission, major changes in its traditional procedures are being openly discussed.

In watching these discussions there is one vital fact that the public needs to keep in mind. Without stringent scientific trials a drug can be used for many years before it is learned that it often **causes** death. "Faster, more humane" access, therefore, can slow progress and be more inhumane.

Regardless of what the FDA decides, it can be certain to generate a storm of dissent from one group or another. Somehow that governmental body needs to walk a tightrope somewhere between faster approval for drugs and protection from harmful ones and at the same time avoid a return to the days when anyone could sell rhinoceros horn — or laetrile — from the trunk of an automobile. Change for the sake of change is not enough.

# *Back and Leg Pain*

*(Continued from Page 1)*

probably less than five percent of such patients have associated leg pain (sciatica) on the basis of nerve root irritation.

Dr. Robert J. Boyd, an MGH orthopedic surgeon and a specialist in back pain, said pressure alone on a nerve root may weaken muscles served by that nerve, but the sensation may be no more than a tingling.

"Sciatica occurs when there is pressure on an inflamed nerve root," he said. "If I pressed on the skin of my arm, there would be no pain. If I pressed hard enough, I might feel a numbness. But if I developed a bad sunburn, the area would become inflamed as part of the body's healing response. Any pressure then would hurt, just as it does in sciatica."

In severe instances, sciatica can cause loss of leg reflexes and the wasting of calf muscles.

The vertebrae comprising the spinal column are fashioned like building blocks, one atop another. Each wafer-like disk separating the vertebrae and giving elasticity to the column consists of a ring of cartilage with a pulpy center.

Accumulated stresses from the physical demands of a job or simply from aging can cause the disk lining to thin and lose its resiliency.

Dr. Boyd cited the 18-year-old youths who dive into the churning ocean from the high cliffs at Acapulco, Mexico.

"Even though their hands hit the water first, the head of each diver sustains a heavy impact," he said. "Because of the repeated trauma, X rays of the divers' necks would give the impression that they were very old people.

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"So it's not only age but how the parts of the spine have been used or abused. Construction workers, piano movers, loggers, and boxers are more likely to get degenerative changes in the lower back than others whose activity is less strenuous."

If the ring of an intervertebral disk ruptures, the pulp in the center can escape and press against nerve roots in the spinal canal, which runs inside the spinal column.

Although the ensuing pain may travel as far as the toes, treatment for a ruptured, or herniated, disk in at least 90 percent of patients is basically rest in a bed that offers firm back support, application of a heating pad or hot water bottle, and pain-relieving medication.

*In this model, a ruptured spinal disk can be seen squeezing out from between two vertebrae (See arrow) and pressing against nerve roots in the spinal canal.*

"The whole disk does not slip completely out of place," said Dr. James R. Lehrich, Director of the MGH's Neurology Ambulatory Care Unit. "Usually only a small part protrudes and presses on a nerve. Relieving pressure on the disk allows it to dry up a bit, get somewhat smaller, and then retract."

When a large amount of a disk presses on a nerve, surgery may be necessary. Whereas a physical examination and the patient's history had usually been adequate for a diagnosis earlier, specialists must now turn to an MRI (magnetic resonance imaging) or CT (computed tomography) scan or to a myelogram (an X ray of the spine after contrast material has been injected) to find out exactly what is going on, where, and what must be done.

An operation by an orthopedic surgeon or a neurosurgeon to repair a ruptured disk provides good pain relief to some 95 percent of patients, but Dr. Boyd said there is a 5 to 10 percent chance that the rupture will some day recur.

When a bone spur from osteoarthritis protrudes into the spinal canal and presses against nerve roots, bed rest with other simple care, just as for a ruptured disk, is usually all the treatment that is needed.

"Bone spurs don't come on suddenly," said Dr. Lehrich. "Something must have shifted to irritate a nerve and make it inflamed and swollen. Bed rest takes pressure off the nerve and allows the swelling and inflammation to subside, thereby relieving the pain."

Diabetes commonly leads to painful nervous system disorders (neuropathies), and sometimes the sciatic nerve may be involved. The most frequent diabetic neuropathy affects nerves in the feet, causing burning or numbness.

There is another form of diabetic neuropathy which affects larger nerves high up in the legs. The pain that results may mimic sciatica. Diabetes can even affect nerve roots themselves as they pass out of the spinal canal.

"If a diabetic neuropathy causes sciatic pain, bed rest usually won't help," Dr. Lehrich said. "The treatment is to bring the diabetes under control while relieving the pain with appropriate medication. In time the symptoms of the disorder should subside."

The sciatic nerve sometimes draws the attention of gynecologists. During pregnancy, women may complain of occasional sharp pains. Dr. Isaac Schiff, Chief of Gynecology at the MGH's Vincent Memorial Hospital, said that vertebral and pelvic ligaments become relaxed during pregnancy and if pain develops it is possible that the weight of the unborn infant is putting pressure against the lumbosacral plexus, where the sciatic nerve begins.

Dr. Schiff added that various cancers of the female reproductive tract, such as cervical, ovarian, and uterine tumors, can spread to the sciatic nerve because of the close proximity.

Sciatic pain can provide an important tipoff to the presence of a woman's disorder called endometriosis. Cells in the lining of the uterus, the endometrium, are normally shed from the body when a woman menstruates. On occasion, however, those cells are discovered outside the uterus but in the pelvic cavity.

Dr. Keith Isaacson of Gynecology said that sciatic pain arising during each menstrual period can indicate that bleeding from endometriosis or scar tissue resulting from the disease has irritated the nerve. The pain's cyclic pattern is the chief clue.

"When we suspect that endometriosis is causing sciatica, we will request an MRI exam," Dr. Isaacson said. "The endometriosis can often be seen very close to or directly on the sciatic nerve."

A hysterectomy may be prescribed to cure the malady, but other medical and surgical procedures can be tried in an effort to preserve reproductive function.

The sciatic nerve can suffer direct injury in many ways. If the nerve is severed but the patient reaches a hospital early enough, a neurosurgeon may be able to reconnect the nerve and restore function. If the nerve has simply been bruised or stretched, time alone can heal the injured area.

Some ways in which the sciatic nerve can be disturbed include:

Falling and landing on the buttocks, sitting on one buttock on the edge of a chair, spending too many hours behind the wheel of a car or truck, and even walking, running, or bicycling too strenuously.

Then there is "rich man's sciatica" which comes from carrying a fat wallet in a back pocket. While the owner is seated, the wallet can press on the nerve.

# The Season Nears for an Increase of Foot Infections

WITH THE HOT DAYS of summer drawing nearer, a common disease of urban civilization is about to make its presence felt again.

Most people give little thought to the fungal infection known as athlete's foot. Yet, it is estimated that between 10 and 20 percent of America's population suffer each year from the condition.

The symptoms range from a scaling, cracking, and itching of the skin between the toes to a more diffuse scaling, with or without blisters, on the soles of the feet, also accompanied by itching.

Some individuals with athlete's foot also develop a yellowing of the toenails, a condition called onychomycosis. Accounting for 20 percent of all nail disease, onychomycosis is often very difficult to treat.

During the winter, the dermatology unit in the MGH's Wang Ambulatory Care Center treats about 30 patients a month for athlete's foot. The number of such patients jumps to about 175 a month with the arrival of summer.

Fungi are simple, leafless plants that occupy the lowest rung on the ladder of the plant kingdom. Lacking chlorophyll, they cannot produce their own nourishment so they find it elsewhere by attaching to other plants or to creatures.

Of more than 100,000 species of fungi that have been described, only about 175 encroach on humans. Most of these species limit their invasion to the skin or just beneath it. About 20 types of fungi can cause widespread infections, however. Some are life-threatening.

Athlete's foot (formally known as *tinea pedis*) probably was not common until humans began wearing tight-fitting footwear. First described in 1888, the disorder was found to be most prevalent in civilized, urban areas. Primitive populations, rarely wearing shoes that enclose the feet, seemed spared.

The incidence of infections can be related to the frequency with which people use such facilities as communal baths, swimming pools, gymnasiums, and locker rooms.

Fungi, which thrive amid heat and high humidity, find an excellent abode in spaces between the toes. Close-fitting shoes maintain this optimal microenvironment as the fungi (mainly three strains called dermatophytes) feed on dead skin cells that contain the protein, keratin. This is the same ingredient found in fingernails and toenails.

The symptoms of athlete's foot are not engendered by the invading fungi but by the body's effort to fight off the foreign organisms.

The host's immune response can also be exacerbated in at least a couple of ways.

A cracking, or fissure, in the skin and a blister that eventually breaks can cause bacterial infection. The interaction of bacteria and fungi often produces a more severe, combined reaction.

Studies also indicate that even though dermatophytes grow only on dead skin they apparently release chemicals that penetrate live parts, thereby inducing an inflammatory response.

Avoiding sweat on the feet helps to avert athlete's foot. Measures to accomplish this include drying the feet carefully after a shower, especially between the toes, and sprinkling powder on the feet; donning moisture-absorbing cotton or wool socks, as opposed to synthetics; and wearing leather shoes or sandals because they allow the feet to "breathe."

Even if the fungi were present, they would not grow so easily on the skin if such precautions were taken.

The same dermatophytes that affect the feet can also affect the hands (*tinea manum*), but such an infection is not encountered very often because, unlike the feet, hands are usually uncovered and thus well ventilated. People such as restaurant dishwashers, whose work finds their hands in water much of the time, are among those most prone to fungal hand infections.

Numerous antifungal agents are available, both over the counter and by prescription. Tinactin and Desenex are popular nonprescription remedies. Lotrimin, which requires a doctor's order, is very commonly used and, like some other agents, comes in a variety of preparations.

When athlete's foot involves the toenails where topical treatments are not effective, dermatologists often turn to griseofulvin, an oral medication developed many years ago. While very useful in treating dermatophyte infections, however, only about 20 percent of patients with yellowed nails will find this condition cleared even after taking griseofulvin for up to a year.

Since onychomycosis is mainly a cosmetic problem, use of the drug can be terminated at any time. Fungal nail infections are almost exclusively an adult illness. Children can become infected during household outbreaks, but the faster nail growth in children appears to make them more resistant to the infection.

"New topical drugs to clear nail infections are now being tested," said Dr. Ernesto Gonzalez, an MGH dermatologist and Assistant Professor of Dermatology at Harvard Medical School. "Some investigators have very high hopes that the drugs will be a success."

In recent years, the immunosuppression of patients to avert rejection of a donated organ and the damaging effect on the immune system caused by AIDS have raised concerns about certain fungal infections.

"Some infections once considered fairly benign are now becoming much more severe in terms of dissemination," Dr. Gonzalez said. "Even dermatophytes, which are supposed to be confined to the skin, have disseminated in people whose immune system has been suppressed and have produced fatal consequences."

Most disseminated fungal infections occur because of inhalation of the spores. They lodge in the lungs and sometimes spread from there to other organs.

Histoplasmosis is such a fungal disease. Labeled an opportunistic malady, it often infects people who explore caves where the fungus grows wild. In an otherwise healthy person, the disease may be transient or self-limited, but in someone with a compromised immune system, histoplasmosis can attack almost any organ in the body and prove fatal.

Dr. Gonzalez said there has been an increased incidence of another fungal disorder, cryptococcosis, among immunosuppressed patients, particularly persons with AIDS.

"Cryptococcosis has a marked tendency to invade the central nervous system," he said, "but in AIDS patients especially the infection has often started with skin involvement instead."

Not only can that course tend to delay a definitive diagnosis and the start of treatment, but cryptococcosis can also mimic tuberculosis, cancer, brain tumors, and even insanity.

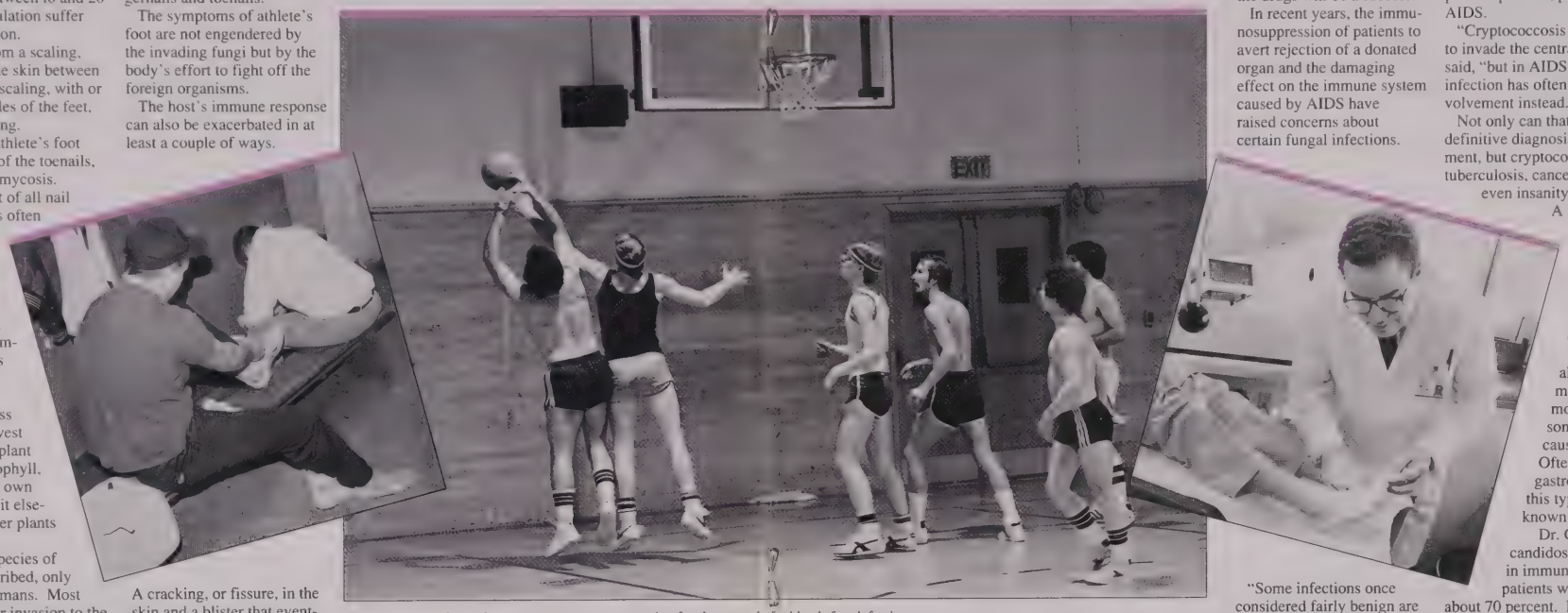
A fungal disease very prevalent in women is a yeast infection called candidosis. It commonly involves the skin and nails and leads to inflammation of the vagina.

Candidosis may also infect mucous membranes in the mouths of infants (and sometimes of adults), causing whitish spots. Often accompanied by gastrointestinal irritation, this type of candidosis is known as "thrush."

Dr. Gonzalez said that candidosis can disseminate in immunocompromised patients with a mortality rate of about 70 percent. But in AIDS patients, dissemination rarely occurs even though they are immunosuppressed. Presumably these patients develop antibodies that protect them against candidosis.

Dermatologists have high regard for the effectiveness and safety of the many drugs available over the counter and by prescription to combat athlete's foot and, to a lesser extent, for systemic drugs that are used to treat the more serious fungal infections. But the treatments do not always assure permanent relief.

Since recurrences are common, the importance of adopting simple, regularly followed practices to prevent an infection in the first place cannot be overemphasized.




***Left:*** *Locker rooms are a common setting for the spread of athlete's foot infections.*
***Center:*** *Working up a sweat in a fast-moving game can create optimal conditions between the toes for attracting fungi.*
***Right:*** *Dr. Ernesto Gonzalez examines the feet of a patient in the Ambulatory Care Center's Dermatology Unit.*

# *Skull Undisturbed by Magnetic Stimulation*

*(Continued from Page 1)*

eration impossible.

The new device, called a Transcranial Magnetic Stimulator, overcomes these problems and painlessly provides highly accurate numerical data on motor system status. The technique was developed by a research team at Sheffield University in England.

In addition to being studied in various parts of Europe, the method has federal Food and Drug Administration approval for patient care trials in a handful of American medical centers, including the MGH.

The British research group, led by a physicist, Anthony Barker, showed that by using an electric coil capable of generating a brief magnetic field they could stimulate the motor part of the brain's cortex without disturbing the scalp or skull. The motor cortex is the principal part of the brain responsible for producing the movements that a person wants to make.

With an EMG (electromyography) machine hooked up to a muscle to record its electrical activity, the stimulator is placed on or slightly above the patient's head and is then pulsed. The EMG machine records the exact time it takes for the muscle to twitch after the stimulator is activated.

By testing many healthy people with the instrument, investigators have been able to determine how long it should take for the electrical currents to move through the nerve pathways.

"Going too slowly through the pathways or not at all would indicate a disturbance of some kind in the motor system," said Dr. Chiappa, who is also Associate Professor of Neurology at Harvard Medical School.

"The information we get in our test does not tell us by itself what disease might be present. But when you add the new data to the bigger picture that includes other information, perhaps from sensory studies, MRI (magnetic resonance imaging) scans, and the patient's history and physical examination, the chances of arriving at a definitive diagnosis vastly improve."

After the diagnosis and the start of treatment, the magnetic stimulator can again be used to monitor the patient's response to care.

The magnetic stimulator is a donut-shaped device equipped with a handle. The instrument's peak power virtually equals the magnetic strength in a huge MRI scanner, but unlike the scanner the stimulator remains at that peak level for only an instant.

The strength of the stimulator's magnetic field is not diminished or otherwise altered by having to pass through the scalp and skull. In contrast, because of the skull's thickness, any attempt to electrically stimulate the brain's motor cortex requires uncomfortably high voltages.

In using the magnetic stimulator to test a patient for possible ALS, neurologists found to their surprise that they could not produce a muscle twitch in the person's hand even though the patient could move the hand at will.

Dr. Chiappa said two theories were offered. Perhaps the hand muscle could not twitch because the targeted neurons, or nerve cells, in the motor cortex were the first ones damaged in the disease process. Or perhaps the neurons that were stimulated were not the same ones that people normally use for casual hand activities. The stimulated nerve cells could have been larger ones which people usually reserve for strong or very fast movements.

Unlike ALS, the cells in the cortex are all intact in patients with multiple sclerosis. The lesion, or damage, from this disease develops farther down in the spinal cord. Thus, the electrical signals start out normally but then cannot get past the spinal cord blockage.

At a recent neurological meeting in Montreal, Dr. Chiappa learned of a high school football player who was dumped on his head during practice and later claimed that he could not move his arms and legs.

Physicians could not find any paralysis, however. A magnetic stimulation test produced perfectly normal responses. The greatest fear after the fall had been the possibility of spinal cord damage, but without the magnetic stimulator there would have been no artificial means of activating the motor part of the cortex to check this out and verify the clinical impression of a psychological disorder.

At some centers, magnetic stimulation is being used to monitor patients during spinal cord surgery. In the past, the sensory tracts have been followed during such operations, but the normal functioning of sensory nerves after surgery does not assure that the motor pathways have also emerged problem free.

Dr. Chiappa said that some researchers are using the magnetic stimulator to study areas of the brain associated with cognition. The psychological experiments are aimed at uncovering clues to how the brain functions during thinking processes and where deficits may lie.

The question of safety in using the

*An electric coil held over a man's head by Dr. Keith Chiappa generates a magnetic field when pulsed and this stimulates a part of the brain responsible for signaling muscles. A recording of how well nerves transmit the signals can reveal nerve disorders.*

magnetic stimulator has been considered at great length by the MGH team which, in addition to Dr. Chiappa, includes Dr. Bhagwan T. Shahani, Director of the Clinical Neurophysiology Laboratory; Dr. Didier Cros, Director of the EMG Laboratory; Drs. Bruce Day, Richard MacDonnell, Barbara Shapiro, Jane Achenbach-Ng, and Nicolas Mavroudakis, all Fellows; and Jianjun Fang, a biomedical engineer.

"We're very certain that there is no danger," said Dr. Chiappa. "In fact, I've calculated that it is safer to have this test than to have a conventional EEG exam when perhaps 1 in 5,000 patients suffers an epileptic seizure. To the best of my knowledge, in the world's entire experience with magnetic stimulation, a seizure has occurred only once."

Neurologists have also looked at electroconvulsive therapy (ECT), so-called shock therapy. In ECT, a tremendously greater amount of current is passed into the brain than with magnetic stimulation and even that higher amount of power has not been found to produce epilepsy in the long term.

Candidates for magnetic stimulation are not accepted if an electronic device, such as a cardiac pacemaker or an insulin infusion pump, has been implanted in the body. Patients with internal metal clips or plates are also excluded.

Actually, the magnetic fields are very narrowly focused in the cortex and are limited in strength. During stimulation, the physician positions the magnet only an inch or so from the motor cortex. Dr. Chiappa's group generally produces just enough magnetic activity to carry out the test.

To further illustrate the safety of magnetic stimulation, Dr. Chiappa pointed out that alcohol can have a toxic effect on the brain. He said:

"A person with time to spare would probably be better off as far as his brain is concerned if he came by for a magnetic stimulation test than if he dropped into a bar for a drink or two."

# *Hiccups: As Many Causes As Treatments*

EVERYBODY DOES IT at some time or another, although the reason is not always clear. And everybody has a remedy to offer, but there really isn't one that works for all.

To most people, a hiccup is a momentary experience, occasionally a social embarrassment, but in general a reflex that is quickly overcome and forgotten, like a cough or a sneeze.

Not everyone is so fortunate, however. It is not unheard of for hiccups to persist for days, even weeks, causing inability to sleep, loss of appetite, and a marked weight drop.

In 1989, *The Guinness Book of World Records* reported on an Iowa man who had hiccuped 12 times a minute, or nearly 18,000 times a day, for more than 66 years. Nobody knew the cause.

Another fellow hiccuped an estimated 160 million times during an eight-year period. He lost 64 pounds.

Physicians have talked about hiccups since ancient times. Hippocrates cautioned that "in inflammation of the liver, hiccough is bad." Galen, another noted Greek physician, suggested that hiccups were caused by "arousing the stomach to violent emotions."

The Greek philosopher Plato came up with the idea of "scaring away" hiccups with a good whack on the back. The causes of and treatments for hiccups have turned out to be so numerous that today a patient with persistent hiccuping may wind up being treated by a pulmonary specialist, a gastrointestinal expert, or a neurologist.

Hiccups occur when the diaphragm, a large, powerful, dome-shaped muscle at the base of the chest cavity, contracts suddenly. The spasm sucks air into the lungs, then stops abruptly. This causes an audible closure of a protective, lidlike structure (the epiglottis) whose function is to prevent food from entering the windpipe during swallowing.

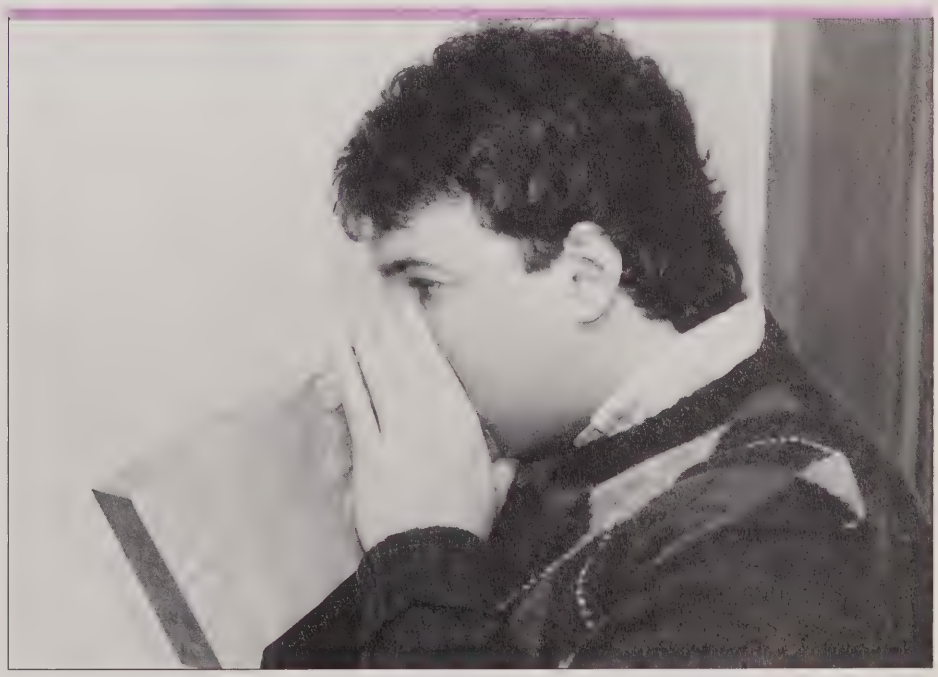
Among the most common causes of short-term, self-limited episodes of hiccuping are distention of the stomach due to overeating or excessive drinking of carbonated beverages, exposure to sudden temperature changes, such as taking a cold shower or going from a heated room into a cold one; sudden excitement or emotional stress, and consumption of alcohol (which can damage the liver, thus supporting the conclusions of Hippocrates that hiccups are associated with liver problems).

A persistence of hiccups for more than two days often signifies the presence of an underlying illness.

A study of 220 patients with intractable hiccups seen at the Mayo Clinic between 1935 and 1963 showed that among 181 male participants 93 percent had organic problems while 7 percent had emotional or psychological difficulties.

In contrast, among 39 females in the study only 8 percent had organic disorders and 92 percent had psychogenic

*(Concluded on Page 8)*



*One popular hiccup remedy is to breathe into a paper bag, reinhaling expelled carbon dioxide. For safety reasons, children should not undertake this technique without adult supervision.*

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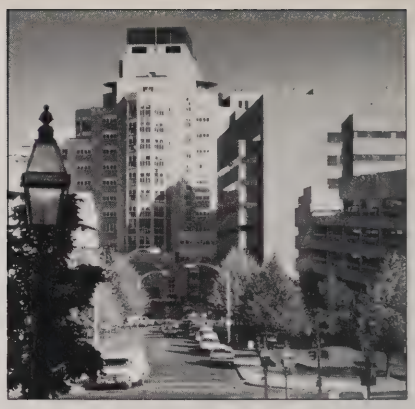


# *Hiccups Often Yield To Home Remedies*

*(Concluded from Page 7)*
disturbances, including addiction, anxiety, bed-wetting (enuresis), an eating disorder (anorexia nervosa), and malingering.

Researchers agree that persistent hiccups affect many more males than females, but they cannot explain why.

It has been known for many years that hiccups result primarily from spasms of the diaphragm, the main muscle used for breathing. Since the phrenic nerve carries the brain's instructions to the diaphragm, some doctors have attributed the spasms to probable irritation of the nerve. They have sometimes been successful in curbing intractable hiccups by inhibiting the nerve surgically or with an anesthetic.

It has also been postulated that tumors or inflammatory lesions in the brain may trigger hiccups by affecting centers there which control the respiratory muscles.

In the opinion of some practitioners, hiccups also may be generated in the fleshy mass of tissue (uvula) which hangs from the center of the soft palate above the back of the tongue.

One reason for this theory is that stimulation of the soft palate and the throat (the pharynx) with a cotton swab or some similar object will often terminate an episode of hiccups.

There may be more than 100 causes of hiccups and almost as many proposed treatments. Many drugs have been prescribed. Some, such as Thorazine, Ritalin, and Tegretol, have proved beneficial.

Most medications have potential side effects, however. Dr. Douglas C. Johnson, Director of the MGH's Pulmonary Function Laboratory, said he recommends first trying a remedy that is unlikely to have side effects.

He told of an MGH patient who had suffered from hiccups for two weeks. Dr. Johnson had the man brought to the Pulmonary Function Lab to breathe five percent carbon dioxide ($CO_2$) for about 15 minutes. At the same time, the patient received extra oxygen as a safeguard against his own oxygen levels falling too low.

"Carbon dioxide is a very strong stimulus to breathing," Dr. Johnson said. "$CO_2$ will cause the frequency of the breathing rate to accelerate dramatically."

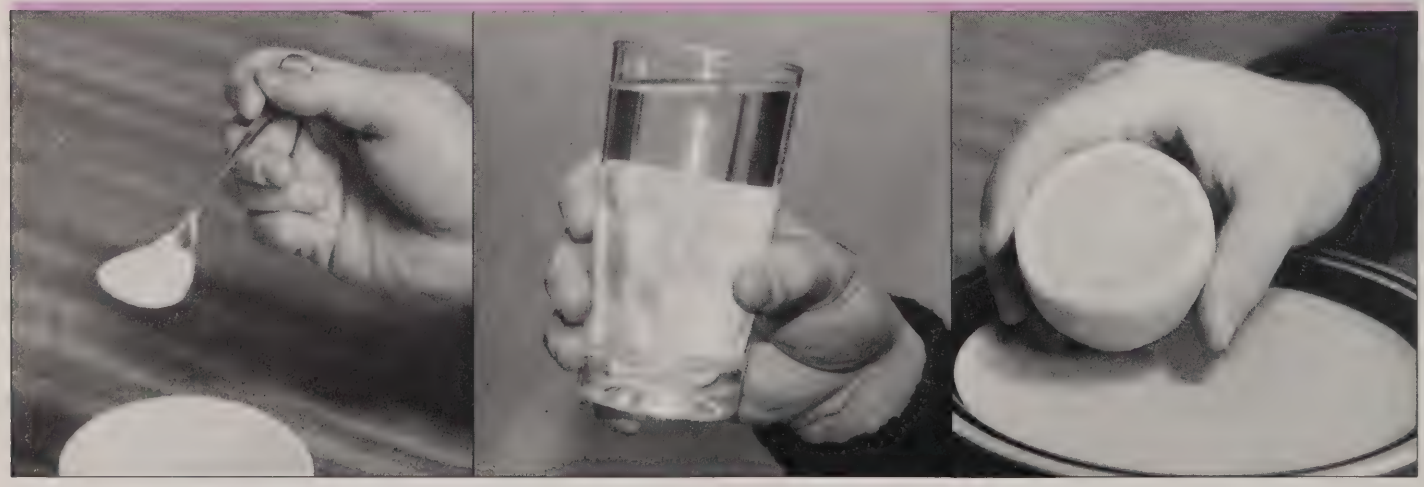
Although the patient's treatment lasted 15 minutes, his hiccups ended after 10 minutes of breathing the carbon dioxide.

People with hiccups commonly try to stop them by covering the nose and mouth with a paper bag and then breathing into the bag. What happens is that the carbon dioxide exhaled by the individual is taken back into the lungs. Although this method may sometimes work, Dr. Johnson cautions against breathing into the bag for very long to avoid dizziness and even unconsciousness from oxygen depletion. Children should not attempt this procedure without adult supervision.

Other common home remedies that might just work include:

- A series of deep breaths;
- Swallowing a teaspoonful of dry granulated sugar;
- Drinking as much water as possible in a single gulp;
- Sucking on a lemon;
- Swallowing dry bread;
- Inducing a gasp with some noxious substance such as smelling salts;
- Pulling the knees up to the chest or leaning forward to compress the diaphragm.

Several research teams have reported the successful use of hypnosis in treating persistent hiccups. And in the Far East, it is said that acupuncture has long been used to deal with the problem. ■



*Swallowing a spoonful of dry granulated sugar can sometimes terminate an episode of the hiccups. Or sometimes drinking as much water as possible in a single gulp will work. And sucking the tart juice from a lemon may do the trick too.*

MGH News

Massachusetts General Hospital, Boston, Massachusetts

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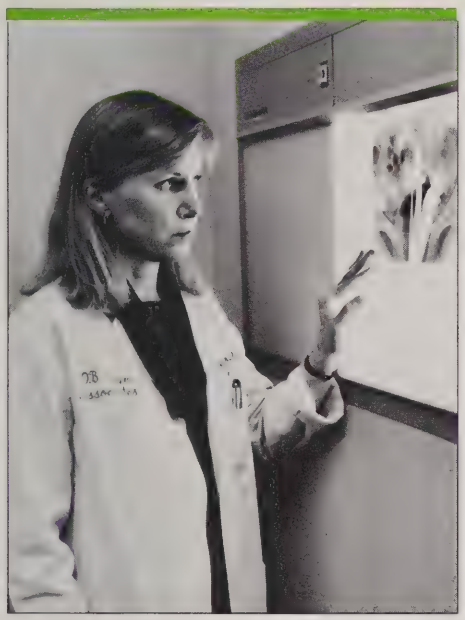
# New Help for Menopausal Problems and Infertility



*Dr. Veronica Ravnikar, Director of the new Vincent Gynecology Infertility and Menopause Service*

THE Vincent Memorial Hospital, the women's care division of the MGH, has established a unit to serve women who have menopausal disorders and to assist couples trying to overcome infertility.

Dr. Isaac Schiff, Chief of the Vincent Memorial Gynecology Service at the MGH, announced the appointment of Dr. Veronica A. Ravnikar to direct the Vincent Gynecology Infertility and Menopause Service.

Dr. Ravnikar came to the MGH in January from Brigham and Women's Hospital in Boston where she was in charge of the menopause unit as well as the in vitro fertilization program.

Working closely with Dr. Ravnikar at the MGH are Dr. Schiff and Dr. Keith B. Isaacson, who joined the Gynecology Division last September after completing a Fellowship training program at the University of Pennsylvania.

Fourteen years ago while at the Boston Hospital for Women, now a part of Brigham and Women's, Dr. Schiff established what was probably the first Menopause Clinic in the nation.

*(Continued on Page 4)*

## *Gaining a Toehold on Pancreatic Cancer*

CANCER of the pancreas....

The words terrify, and considering the startling statistics associated with this disease, the emotional impact is understandable.

The American Cancer Society estimates that 28,100 Americans will be diagnosed this year as having pancreatic cancer and that 25,000 people will die of the dreaded disease before the year ends. The society says that only three percent of patients with this illness live more than five years after diagnosis.

*Despite the ominous picture, however, medicine is gradually improving the outlook.*

Situated deep in the abdomen, behind the stomach, the pancreas, an eight-inch-long rather elliptical organ, performs two vital tasks. It produces insulin to control sugar in the blood and enzymes needed to aid digestion.

The only present possibility of curing pancreatic cancer is to surgically remove the tumor. But only about 10 percent of the cancers found in the head of the pancreas (the part through which the common bile duct passes) might be removed; that is, they have not yet spread (metastasized) from the primary site or grown too large.

Cancers in the body and tail of the organ can very rarely be removed for potential cure.

No good screening tests are available to reveal pancreatic cancer in its

*(Continued on Page 2)*

## Youngsters Who Have "No Head for Figures"

MUCH has been written about the dyslectic child who cannot process information in an organized fashion, uses words out of sequence in sentences, and cannot spell or even form letters properly.

Many notables, among them Thomas Edison, Leonardo da Vinci, Winston Churchill, and Albert Einstein, suffered from dyslexia during childhood.

While this condition has been described in detail, there is another childhood learning disorder about which precious little has been written. It embraces youngsters who learn to read and write perfectly well and are normal in every respect, save one.

They have what doctors call "developmental dyscalculia." To put it another way, they have no head for figures.

"Neurologists have recognized dyscalculia for almost as long as dyslexia," said Dr. Peter B. Rosenberger, an MGH neurologist and pediatrician who directs the hospital's Learning Disorders Unit.

"The ability or inability to do math has been used in the past as a bellwether for general intelligence. If a child did well in math but poorly in reading, it was felt he had a specific learning disorder. If he fared poorly in both, then maybe he was

*(Continued on Page 6)*

## INSIDE:

**Page 7** — Don't rush to pin on the allergy label.

EDITORIAL

# Made of His Father's Stock

DR. CHARLES E. HUGGINS was not your typical famous man's son. His father, Dr. Charles B. Huggins, of Chicago, is a cancer scientist. His research won him a Nobel Prize.

So often, it seems, the sons of prominent men have a difficult time finding themselves. Perhaps the dread of falling far short of their fathers' achievements drives them into other fields. Still the comparison with their fathers haunts them. You know. "He's a nice lad, but he's not made of his father's stock."

Charlie the younger risked comparisons by choosing a career in medicine. The Chicago native was only 23 years old when he earned his M.D. cum laude from Harvard Medical School. He trained in surgery across town at the MGH. But it was the year at London's National Institute for Medical Research that focused him on low temperature biology. Years later in his droll way he told a medical writer that his mentor there said, "Huggins, freeze blood." And he did. Until that achievement, physicians had 21 days to transfuse blood— or discard it. Scientists had experimented with freezing it. The problem was finding a practical way to thaw it. In 1960, the year of his return to the MGH, young Dr. Huggins began his quest. He developed in 1963 a device known as the Huggins Cytoglomerator. Until he retired it last year, after improved mechanisms became available, it gave the MGH and many other hospitals freedom from worry. Instead of a 21-day shelf life they could store blood indefinitely.

Charlie (everyone called him that) found some innovative ways to use the Cytoglomerator. About three years after its development, MGH cardiac surgeons were confronted by an unusual problem. A young Maine boy needed open heart surgery. Open heart surgery then required (and frequently still does) donated blood to replenish what is lost or damaged during the operation. The trouble was that there were but a handful of persons in the world — none in the United States — known to have a special factor found in the patient's blood. The solution was the Cytoglomerator. For many months before the scheduled surgery, the boy began donating a unit of blood to himself. When enough was frozen, cardiac surgeons operated with the security of the youngster's own blood in readiness.

From 1973 until his death on April 18, Charlie Huggins directed the MGH's Blood Transfusion Service and made it a world leader. He turned in recent years to the conservation of blood, stressing it should be transfused only when it was unequivocally necessary. He taught surgeons how to preserve blood in the operating room. With techniques developed at the MGH and elsewhere, this hospital has been in the forefront of blood banks substituting the patient's own blood for donated units. Through pioneers like Charlie Huggins blood banking has become increasingly safe even as the threat of AIDS and hepatitis have worried the public.

## *Some Pancreatic Tumors Easily Treated*

*(Continued from Page 1)*

earliest stages. By the time symptoms appear, such as pain, weight loss, jaundice, or an inflammation (pancreatitis), most people are considered beyond cure.

Dr. Andrew L. Warshaw, Associate Chief of Surgery at the MGH, spoke, however, of a forward movement against this form of cancer.

"Despite reports that pancreatic cancer increased from 1950 to 1985," he said, "the fact is the rate has stabilized since 1975."

A general surgeon, Dr. Warshaw has a special interest in gastrointestinal disorders, particularly those affecting the liver, biliary tract, and pancreas.

He said nobody knows why pancreatic cancer increased originally and why the rise stopped, but concomitant with the stabilization has been a sharp drop in the mortality associated with the surgery.

Known as the Whipple operation or a modification of it, the surgery involves removal of the head of the pancreas, the first part of the small intestine (duodenum), the lower end of the bile duct, associated lymph nodes, and sometimes part of the stomach.

"The mortality for that operation in many institutions has fallen from 20 percent plus — as high as 40 percent in some hospitals—to well under 5 percent," Dr. Warshaw said. "Our own track record at the MGH is about 1-1/2 percent."

New and improved techniques of surgery and anesthesia have evolved over the last 15 years, he said, but, in the main, concentrating this work in individuals

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who have a wealth of experience doing it seems to make a difference in the result.

Recent reports from a number of institutions, including Johns Hopkins, UCLA, and a center in Kyoto, Japan, have described postsurgical cures of pancreatic head carcinomas ranging as high as 20 percent compared with an earlier rate of only 2 percent.

No one can pinpoint the reason for the improvement, although less blood loss and fewer blood transfusions may be a contributor. Blood transfusions sometimes reduce the body's immune defense and may thus allow a cancer to grow.

Earlier this year, in the scientific journal *Archives of Surgery*, an MGH team comprising Dr. Warshaw and Drs. Zhuo-yun Gu, Jack Wittenberg, and Arthur C. Waltman reported on a study of how accurately various techniques determine whether pancreatic tumors can be surgically removed.

Among 88 patients, the team evaluated the use of CT (computed tomography), angiography (using contrast materials in X raying blood vessels), MRI (magnetic resonance imaging), and laparoscopy (direct visualization of the interior of the abdomen using a scope).

"We found that MRI doesn't help at all in this disease," said Dr. Warshaw, the principal author of the journal paper. "CT and angiography were very effective in identifying tumors that had begun to invade major vessels passing through the pancreas, particularly veins where most of the trouble occurs.

"A main failing of CT and angiography was that they could not pick up multiple small metastases, but it turned out that laparoscopy could provide that information. Overall, 44 percent of our study patients had metastases seen only by laparoscopy."

Even identifying a tumor as inoperable serves a purpose. It avoids major surgery and convalescence that would cut into whatever good time the patient has left.

And sometimes there is an alternative to the surgery. If the patient's primary symptomatic problem results from the tumor blocking bile flow, endoscopic and radiologic methods can now be employed to reopen the obstructed channel.

The tumor itself continues to grow or spread, however. Probably half of all tumors in the pancreas are in the head of the organ.

*Chemotherapy has offered little to the pancreatic cancer patient, but some recent preliminary studies indicate that conventional radiation treatments coupled with surgery may double cure rates. This is being actively explored.*

*Intraoperative radiation, aiming radiation directly at a tumor exposed during surgery, has been useful in treating tumors that are not removable but have not spread. This modality permits much higher doses of radiation to the cancer while protecting nearby healthy tissue.*

*Intraoperative radiation was developed in Japan. Howard University became the first American institution to employ the technique, using it alone as did the Japanese. The MGH was the second American center to adopt the method and pioneered its use as a boost to a conventional course of X-ray radiation.*

Dr. Warshaw said that patients treated with intraoperative radiation survive for a median period of 13 months, a little more than double the normally expected time. And he said that this technique "improves quality of life since it is probably the best thing we've got for pain control."

There is a further important use for radiation. Only a needle biopsy, a taking of tumor tissue for laboratory study, can provide a definitive diagnosis of pancreatic cancer. During manipulation of the tumor with the needle, tumorous cells may be freed to spread through the abdominal cavity.

"During the past five years or so at the MGH, we have made a practice of routinely giving 1,000 rads of radiation prior to biopsy," said Dr. Warshaw. "That is only 20 percent of a normal full dose, but it is enough to kill 99 percent of any loose tumor cells without causing edema [swelling], inflammation, and other things that would make surgery more difficult."

Precise identification of a pancreatic tumor is all important because sometimes the gland contains types of cancers which are much more amenable to treatment and cure. Regardless of the kind of tumor present, the symptoms remain essentially the same.

Dr. Warshaw, who is also Professor of Surgery at Harvard Medical School, said a great majority of cystic adenocarcinomas can be surgically removed with subsequent cure no matter where in the gland they are found.

Ampullary cancer, a type found at the lower end of the bile duct where the duct enters the duodenum, also is a much more curable cancer, he said.

Ampullary cancer, however, can lead to misdiagnosis because it closely mimicks pancreatic head carcinoma. Not only are the symptoms alike, but the two tumors look exactly the same on a CT scan.

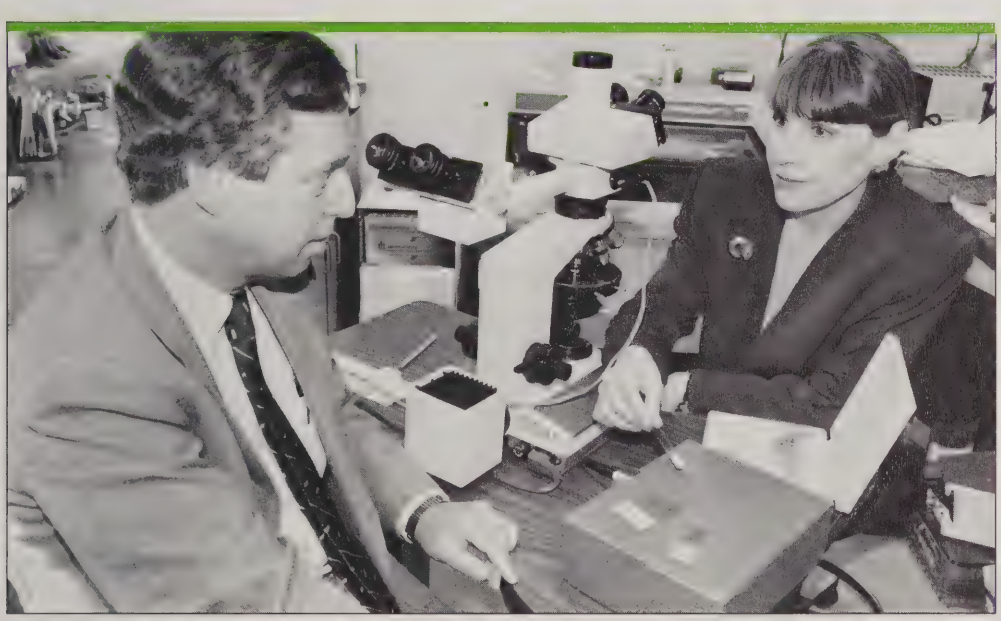
The points at which the bile and pancreatic ducts feed into the duodenum may be only one millimeter apart [the width of a paper clip].

"Biologically, however, these are very different tissues," Dr. Warshaw said. "About 90 percent of the ampullary tumors are operable, and perhaps 35 percent of the patients are cured."

Lymphomas, tumors of the lymph glands, also mimic pancreatic cancer but are treatable. Breast cancer can spread to the pancreas and act like a pancreatic cancer, but breast tumors are much more responsive to chemotherapy.

Dr. Warshaw stressed that any physician suspecting pancreatic cancer in a patient should check out the possibility of it being an alternative, more treatable growth.

"Don't give up too soon," he advised. ■



*Drs. Andrew Warshaw and Carolyn Compton discuss pancreatic cancer studies in Dr. Compton's pathology laboratory.*

# *New Infertility Unit Can Often Boost Conception Chances*

*(Continued from Page 1)*

Since assuming his present duties in April 1988, he has looked forward to organizing the new Infertility and Menopause Service at the MGH.

In the past, he said, health concerns for women have focused largely on quantity of life, or life expectancy. With America's women past 50 years of age now numbering 40 million — an increase of 13 million since 1980 — more attention, he said, must be paid to their quality of life.

In a study sponsored by the National Institutes of Health, Dr. Ravnikar, in consultation with Dr. Robert M. Neer in the MGH's Bone Densitometry Center, has been assessing the bone density of women as they pass through menopause. The hope is to better identify those women who will ultimately be at risk for fractures associated with the bone-thinning disorder, osteoporosis.

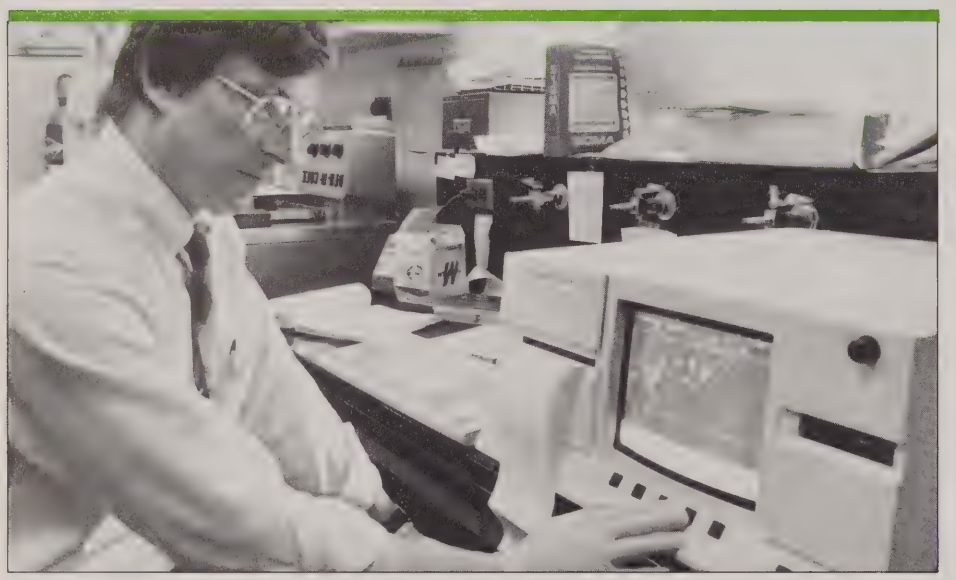
The new Service also works closely with other MGH groups, including the Reproductive Endocrine Unit, directed by Dr. William F. Crowley, Jr., and the Breast Cancer Center, headed by Dr. William C. Wood.

On the subject of infertility, Dr. Schiff pointed out that more and more couples are postponing childbirth until a later age. "This automatically exposes more couples to problems related to infertility," he said. "We intend to do our very best to assist couples in having the children that they desire."

The plans of the Vincent Gynecology Infertility and Menopause Service include establishment of a donor sperm bank and an in vitro fertilization program.

Infertility is a problem for between 10 and 30 percent of couples. The difficulty lies with the husband in 40 percent of such couples, with the wife in another 40 percent, and with both in 10 percent. In the remaining 10 percent, the infertility cannot be explained.

Dr. Ravnikar said that because infertility is a couple problem, her unit sees both husband and wife. Typically, they have been unable to conceive on their own for about a year. Exceptions include couples in their late 30s and early 40s who might have tried to conceive for three to six months and do not want to wait any longer for professional help.



*Dr. David MacLaughlin performs a semen analysis in the Vincent Memorial Hospital's Gynecologic Research Laboratory.*

The Vincent Memorial's Gynecologic Research Laboratory, directed by David MacLaughlin, Ph.D., conducts male fertility procedures including semen analyses and sperm washings.

Dr. Ravnikar said that if the wife's cervix does not produce the right amount of mucus to pick up the husband's sperm, the laboratory can take a sperm specimen, separate it from its seminal fluid, and reconstitute it in a biological fluid in very minute amounts so that it can be inserted into the uterus safely and sterilely.

Inseminations complement ovulation induction therapy introduced by Dr. Crowley's Reproductive Endocrine Unit. His group has made it possible for women to ovulate — to produce mature eggs more efficiently. That and intrauterine inseminations from the husband tend to improve chances for conception.

"Couples who have tried for a year to conceive and have been unable to for unexplainable reasons have approximately a two to five per cent chance of achieving pregnancy on any given cycle," Dr. Isaacson said. "We can increase that to 15 to 20 percent.

"What we're doing is striving to achieve what is usual for a normal individual. We don't have anything better than what Mother Nature can offer."

The in vitro fertilization program being envisioned at the MGH is expected to begin in another year after establishment of a laboratory and the carrying out of a multitude of other details.

Once the program is established, one can think of freezing embryos and doing in vitro fertilization with donor eggs in women who are experiencing a premature menopause or are losing their ovaries.

"The outlook is very promising," said Dr. Ravnikar, who is also Assistant Professor of Obstetrics, Gynecology, and Reproductive Biology at Harvard Medical School.

It will probably take one and a half to two years for sperm to become available from an MGH donor bank to substitute for that of a husband whose sperm count is very low.

The use of fresh donors is frowned upon nowadays because of AIDS fears. By recruiting and testing its own sperm donors, instead of obtaining specimens from commercial banks, the MGH will have much more personal knowledge about the donors and thereby lessen risks. Also the sperm will be held in the donor bank for three to six months before being released.

Dr. Ravnikar said she plans to follow guidelines established by the American College of Obstetrics and Gynecology and the American Fertility Society on the procedures for screening potential donors. The gynecology unit also works with an MGH urologist, Dr. Barbara Bassil, on male fertility. When there is a male structural problem, such as an abnormally dilated vein in the scrotum that can raise the temperature in the testes, sperm motility may decrease. A urologist can usually correct such a disorder.

To help maintain or restore fertility, the new gynecology unit offers the latest

techniques for surgery on the female reproductive tract.

Through a laparoscope, an instrument for visually examining the interior of the abdomen, a surgeon can detect such problems as an ectopic, or out-of-place, pregnancy; endometriosis, an accumulation in the pelvic cavity of cells from the lining of the uterus; and fibroids, benign smooth muscle tumors of the uterus.

After diagnosing a disorder, the surgeon can often use a $CO_2$ [carbon dioxide] or KTP [potassium titanium phosphate] laser to treat the problem through the scope.

*"Every time we detect endometriosis through the scope, we have the laser ready for use," Dr. Isaacson said. "We never look and just leave the condition alone. If it's there, we will treat it. The laser is a very precise and efficient tool.*

> *"We intend to do our very best to assist couples in having the children that they desire."*
>
> *— Dr. Isaac Schiff*

*"Many women with fibroids come to us with recommendations of a hysterectomy. We have the capability to remove the fibroids and still preserve the uterus.*

*"If a woman has a blocked Fallopian tube, we can often clear the obstruction and reconnect the tube microsurgically. Or as an alternative, we can put a catheter through the Fallopian tube to try to open it without major surgery.* An institution that lacks a reproductive unit might not have those capabilities."

During the last 20 years the majority of research efforts on reproductive disorders have focused on the female. But in the past five years or so, a tremendous number of studies have been carried out on male infertility.

Dr. Ravnikar said so many procedures are available today to help the infertile couple that if routine tests by local physicians fail, the patients should think of consulting a specialist. ■

*Using a laparoscope to view the interior of a patient's abdomen, Dr. Keith Isaacson checks for a possible ectopic, or out-of-place, pregnancy. Other members of the operating team follow his progress by watching a monitor carrying televised pictures.*

# *Broader Insights into Math Underachievers*

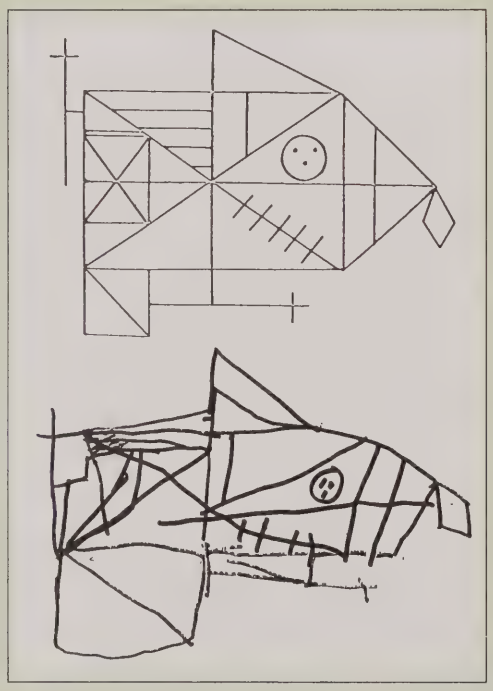
*(Continued from Page 1)*

just stupid. We now appreciate that it is possible to do poorly in math and not be stupid."

Dyslexia affects between three and five percent of America's population, generally more boys than girls. No one knows the incidence of dyscalculia, but Dr. Rosenberger said that as many as one person in ten could have dyscalculia.

He said, however, that it is probably less disabling than dyslexia:

"If you can't learn math in school, you can somehow get around it. If you fail a few math courses, you get excused from a few others, and you're out of it. But if you can't learn to read, you'll find yourself out of luck in school. You won't be able to learn anything."



*To test his abilities at spatial calculating, a 9-year-old youngster was asked to copy the complex figure shown at top. The result, at bottom, showed he had much to learn.*

In India, dyscalculia is much more of a social stigma than it is in the United States. Schools in India place considerable emphasis on the ability to calculate.

To gain a broader understanding of math underachievers, Dr. Rosenberger studied 72 such children who had come to his unit for care and compared them with 30 dyslectic youngsters comprising a control group.

At an average age of 12, the dyscalculics were significantly older than the dyslectics, who averaged 9 years. Children having trouble with math appear to be recognized at an older age than those with reading difficulties.

The two groups were highly comparable, however, in overall intelligence. In the scoring of an IQ test, 100 is considered the norm. The dyscalculics scored an average of 104 and the dyslectics, 105.

In addition to obtaining a complete history on every patient in the two groups, Dr. Rosenberger had each youngster undergo a thorough neurological examination and then take several tests which measured perceptual and language abilities as well as achievements in basic school-related functions.

In a report on the study published in the *Annals of Neurology*, Dr. Rosenberger cited three major findings:

1. The dyscalculics had more attention span deficits than the dyslectics.
2. The dyscalculics had more difficulty than dsylectics in copying complex figures and in spatial calculations, such as dividing a circle into three parts.
3. The dyscalculics exhibited more often a preference for the right hand and right foot but left eye. The norm is to prefer the same eye as the hand and foot.

Regarding this characteristic, Dr. Rosenberger said it may not be so much a deficit in the brain as an atypicality in the brain's organization.

"There may be something atypical about the way the two hemispheres of the brain work together," he said. "We were surprised to find it more prevalent among the dyscalculics than among the dyslectics. We might have predicted otherwise because it's been shown many times among the dyslectics. Possibly one hemisphere controls the hand and foot and the other side the eye."

It has also been suggested in neurology that handling complex numbers is a function of the left hemisphere of the brain while spatial or geometric calculations are accomplished by the right hemisphere.

During preschool years, most dyscalculics learn to count without difficulty. And in their early school grades they make good progress learning to add and subtract single numbers. It's when they are later confronted with double numbers that they run into trouble. Calculations that require "borrowing" and "carrying" confuse them. They cannot proceed to multiplication or division because they find the work too complicated.

*Where it goes from there varies. Some people who have no trouble at all with basic arithmetic turn out to have a terrible time with higher math. But then, there are brilliant theoretical mathematicians who carry a calculator around because they cannot do basic operations.*

So at some point things change. It is suspected, for example, that to learn algebra really requires more language than math skills. "What else calculus requires when you get into that is anybody's guess," Dr. Rosenberger commented.

There is no evidence that dyscalculia is inherited, but Dr. Rosenberger, who is also an Assistant Professor of Neurology at Harvard Medical School, said he would not be surprised if genetics is indeed involved because this has been well established in dyslexia.

The extent to which dyscalculia can affect a person's life depends on two factors: the severity of the disorder and the nature of a chosen career.

"If the person is not going to proceed beyond high school and intends to earn a living at a job that does not involve dealing with figures, the dyscalculia will have little impact," Dr. Rosenberger said. "But if he decides to go on to college, he will have to satisfy some math requirements in most places in order to be accepted, so his life will definitely be affected in that regard."

Dr. Rosenberger stressed the importance of remedial instruction in the lower grades for math underachievers, either alone or in small groups, to help them understand concepts better and give them extra drills.

Will they be able to learn? "Basically, yes," he said. "What we're dealing with in learning disabilities is really a talent deficit in the face of which a skill is harder, but not impossible, to achieve.

"When I explain this to children and their parents, I tell them about trouble that I had learning to play tennis. I've always had zero talent for hitting a ball with a stick. But I developed an interest in tennis. I got the best coaching that I could, and I worked hundreds of hours at the game. I'm now a passable player, but

when I'm on the court I still think of every swing, every step, every move.

"My opponent, who beats me, does not think of every swing and step. He doesn't have to work to acquire his skill. His talent is already wired in.

"I think that is the problem in learning disabilities. People with a talent deficit simply need to work harder to acquire a desired skill."

Remedial instruction, the neurologist added, should be accompanied by curriculum support to keep the child alive academically while he tries to overcome his deficit. At the same time, there should be supportive help to develop other skills that will let the youngster shine and have a better self image.

Most school systems, Dr. Rosenberger said, make a valiant effort to go along with such recommendations. He said he has seen children with proper help conquer difficulties with basic calculations in their early years and go on to higher math without any further obstacles because they had been able to master the arithmetic.

"It's more than likely that people who know they have trouble with a particular skill will stay away from vocations that stress that skill," he said, "but I have had a number of patients with early math problems who today are competing well in first-rate colleges." ■

# *Don't Rush to Pin on the Allergy Label*

Food is not only a necessity but also a source of much enjoyment. Thus, people readily empathize with those who must avoid certain foods because of such concerns as weight, cholesterol, or allergies.

A significant segment of the population is especially deserving of empathy but usually escapes public notice. These are people who claim they are allergic to particular foods but who really are not.

Whether induced by self-diagnosis or improper or incomplete medical testing, the mistaken conviction can lead to years of unnecessarily shunning literally scores of once-enjoyed foods for fear of a reaction. Some of the foods that are shelved are vital for well-balanced nutrition.

In children, dietary restrictions of such magnitude can be especially dangerous since they might very well stunt normal growth and development.

Simply stated, a food allergy is an overreaction by the body's immune system to foods that most people tolerate well. If a person eats a food to which he is allergic, immunoglobulin E (IgE) antibodies being produced by his immune system because of the allergy will react, attaching to so-called mast cells in areas of the body most vulnerable to foreign substances, such as the intestinal tract or the mucous lining of the nose, mouth, or throat. This sets the stage for a clash between the antibodies and the allergen, the guilty party in the consumed food.

During this action, the body releases histamines and other chemicals which produce classic allergic symptoms. These may include a swelling of the lips and tongue, an itchiness over a wide area of the body, a flushing of the skin, and a variety of gastrointestinal discomforts, including pain and diarrhea.

At its severest, the allergic reaction may cause a phenomenon called anaphylaxis in which the patient may develop a swelling of the throat, blocking the intake of air, and may go into shock (a precipitous fall of blood pressure). Anaphylaxis is fortunately a rare event, although it can come from nonfood such as a bee sting.

*No one knows how many Americans are allergic to foods, but researchers believe that more adverse reactions result from an intolerance rather than a true allergy.*

The intolerance may stem from something added to a food, a deficiency of an enzyme needed to convert a food for use in the body, a form of food poisoning, or a psychological hangup in which a person convinces himself that, "if I eat that food, I'll get sick."

Take sulfites, a group of food preservatives. Up to one million Americans cannot eat foods treated with sulfites without suffering adverse reactions. Three quarters of those affected are asthmatics.

Alarmed over the incidence, the federal Food and Drug Administration (FDA) issued an order nearly four years ago prohibiting the use of sulfites on fresh fruits and vegetables.

The order did not ban the preservatives on other foods, such as sauces, baked goods, frozen, canned, or dried seafoods; or beer, wine, and cocktail mixes, but the FDA later ruled that if a food contained more than a set amount of a sulfite, it had to be listed on the label as an ingredient.

Many people cannot drink milk without becoming ill. It is estimated that more than 70 percent of the world's population, including 80 percent of all Black people, are unable to tolerate milk sugar (lactose) because they lack an enzyme (lactase) needed to help break down the milk sugar for proper digestion (*MGH News*, November 1982).

The continued presence of the lactose allows bacterial changes to occur which result in bloating and diarrhea.

"This is a problem which clearly does not have an allergic basis," said Dr. Richard A. Moscicki of the MGH's Clinical Immunology and Allergy Unit. He explained that as most people grow into adulthood their intestines produce less and less lactase. Some northern European ethnic groups are exceptions; they generate lactase well into adulthood.

*(Concluded on Page 8)*

*In the MGH's Allergy Clinic, Barbara Mahoney, RN, administers a skin test to Victoria Davis of East Wakefield, N.H., to determine if she has an intolerance for a particular food.*

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# *If a Food Causes Illness, Cut It From the Diet*

*(Concluded from Page 7)*

High levels of lactose intolerance have been found in eastern Europe, the Orient, Mexico, South America, and Africa. For years, relief agencies wondered why poor people in Africa did not seem healthier after receiving food shipments. It turned out that the shipments included powdered milk which the recipients could not digest.

Overcoming lactose intolerance is not as simple as turning off the milk spigot. Lactose can be found in a variety of foods. It has also been used as a binder or filler in some drugs, including medicines for the heart.

Scombroid fish poisoning can give the false appearance of an allergic reaction. Members of the scombroid family of fishes, such as tuna and mackerel, often contain chemicals similar to histamine. If the fish are allowed to thaw for too long, bacteria can convert the chemicals to a very active form of histamine. When people ingest this, they soon experience allergy-type symptoms.

"When we evaluate such patients," Dr. Moscicki said, "we find that they do not have positive results on allergy skin tests or any IgE antibodies to the fish. The problem is usually traced to improper fish processing."

Less common than scombroid poisoning but a major problem nevertheless is a condition called ciguatera poisoning. Fish which feed on coral sometimes ingest a toxin in the coral. When consumed in turn by humans, the toxin may cause not only an allergy-type reaction but also neurologic symptoms, such as a tingling or numbness around the face or in the hands. On occasion, abnormal heart rhythms may also develop.

Dr. Moscicki said that at present ciguatera poisoning is relatively uncommon in New England, but that this may change since people in the region often eat fish brought in from coral areas of the Caribbean. He said that in the South Pacific as much as 80 percent of island populations in coral regions have experienced ciguatera poisoning.

Many people, especially children, develop a psychological aversion to certain foods. "An unpleasant event occurring at the same time that a certain food is eaten may cause an aversion to that food," Dr. Moscicki said. Psychological counseling can often help a person to overcome such unwarranted concerns.

Occasionally people carry IgE antibodies in their blood and still do not develop allergic symptoms. Dr. Moscicki said that "as children these people probably had an immature intestinal barrier which led to the formation of the antibodies but as their gastrointestinal system matured, they were able to eat any foods without an adverse reaction."

*Many people are unable to tolerate lactose, a sugar in milk and related dairy products, because their body lacks a necessary digestive enzyme.*

In general, a reaction to food due to an intolerance occurs less often and with less severity than a true allergy response, although an asthmatic who ingests a lot of sulfites may suffer a very severe asthmatic episode.

If illness from eating is believed due to an intolerance rather than an allergy, the food in question may simply be eliminated from the patient's diet to see if the symptoms also disappear.

In addition to this withdrawal tactic, a patient suspected of lactose intolerance may be given a special breath test. A device known as a gas chromatograph can determine whether a breath sample contains gases indicative of lactose intolerance.

If, on the other hand, an allergy is suspected and skin and blood tests do not resolve the issue, a third test may be prescribed, provided the patient has not previously experienced life-threatening symptoms from eating certain foods.

Called a double-blind, placebo-controlled challenge, the patient might receive either the suspect food masked in another food, such as apple sauce, or the harmless placebo, an inert substance, to see whether a reaction occurs. Sometimes, instead, the suspect food and the placebo are packed in dehydrated form into capsules. The patient doesn't know which he is served.

A principal form of skin testing today involves placing a drop of allergen extract on the skin and touching that spot with a needle to see if a small swelling or wheal occurs in the skin, indicating a positive test result.

If one injected a suspected food allergen into the skin, the physician said, the allergen might produce a nonspecific irritation which is difficult to interpret. Intradermal injections of food allergens have actually generated anaphylactic shock.

Dr. Mosicki added that using injections of food allergen extract to "desensitize" people to certain foods is not considered an acceptable treatment because the risks of such desensitization in food allergy are not outweighed by the benefits. He said:

"If the patient proves to have a true allergy, then far and away the best and safest way to treat it is simply to eliminate the food from the person's diet." ■

MGH News

Massachusetts General Hospital, Boston, Massachusetts Vol. 49 No. 5 June/August 1990

# Medical Record Keeping Enters the Electronic Age

ONCE HOURS ... now just seconds.

An electronic system for the high-speed delivery of stored radiologic data is moving into high gear at the MGH after six years of development and testing.

Medical record keeping at the hospital entered the electronic era, starting with film records, as the task of storing and delivering needed files on patient care reached physically challenging proportions.

Imagine the results of three million radiologic examinations, including 15 million films, being stored in a single room.

In the Boston suburb of Somerville, the MGH maintains a medical records warehouse with a room spanning half an acre just to hold radiologic files.

When former patients return to the hospital for medical care and requests go to the warehouse for X rays, CT scans, or other studies, anywhere from an hour and a half to three hours elapse before the material arrives by courier at the main campus.

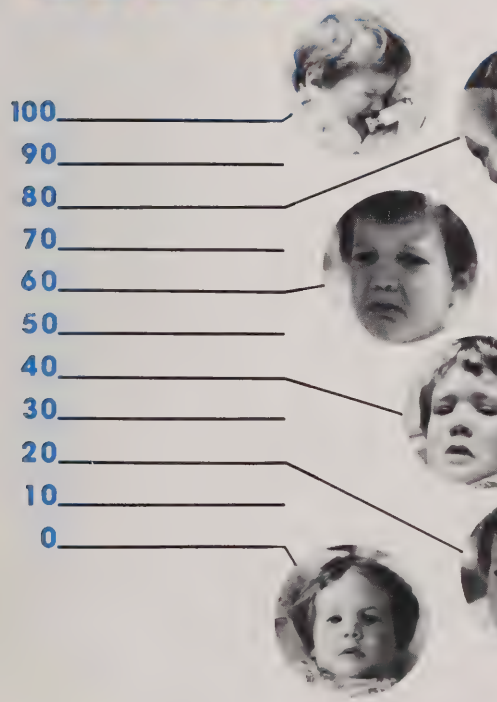
The new technology now being installed at the warehouse will make it possible for X rays there to be converted into digitized, or numerical, form, a process requiring only six seconds, and then transmitted almost instantaneously via fiberoptic cable to the hospital.

The digitized material is converted at the hospital into a high resolution picture displayed on a screen for study. If the physician needs a hard copy of the stored film, the digitized data can simply be fed through a laser printer to recreate the image.

High speed retrieval of imaging material from Somerville is only one component of a remarkable new MGH program called RSTAR (Radiology Storage Transfer Analysis Reporting).

RSTAR consists of a network of stations in various parts of the hospital

*(Continued on Page 4)*




*Using the Oucher scale, children can indicate their intensity of pain by pointing to a facial expression that most closely reflects their discomfort.*

# *Reconsidering a Theory About Pain*

DO ILLNESSES, injuries, or the rigors of major surgery inflict less pain on children than on adults?

Many physicians believe so. But they have been prompted to rethink their position by recent studies which demonstrate broad similarities between the pain experiences of children and those of adults.

The findings reinforce a growing belief that many children, including newborns, have been undertreated for pain in the past.

Speaking at a recent MGH meeting (Children's Service Grand Rounds), Dr. Alyssa Lebel-Schwartz of Pediatric Neurology said that until the last few years the subject of children's pain had been treated with cultural indifference.

She spoke of an investigator's search of the medical literature for articles on pain published between 1970 and 1975. Of 1,380 reports that were found, only 33 — fewer than two and a half per cent — dealt specifically with pediatric pain.

"The reasons for this lack of interest in the pain problems of children ranged," she said, "from erroneous or unsubstantiated beliefs to ethical concerns."

One prominent belief was that the younger the child the less complete would be a sheath of fatty tissue called myelin around nerves. Myelinization permits a rapid signal through a nerve, thus increasing the likelihood of feeling pain.

Dr. Lebel-Schwartz said anatomical studies have shown that nervous system tracts important for pain transmission are almost completely myelinated by the time a baby is born.

In fact, Dr. Elizabeth C. Dooling, another MGH pediatric neurologist, has

*(Continued on Page 2)*

## INSIDE:

**Page 6** — Looking for ways to access the brain

**Page 7** — Drug may give long relief from bulimia

EDITORIAL

# The Dawning of a New Age

Sometimes computers cause as many problems as they overcome. Or even more. Computers do not always save money. They often require more people to interpret the new data they amass. Sometimes, though, the user, whether a hospital or business, cannot afford to hire more employees. In that instance, the device may simply pile up paper and frustrate the user. In either case it is not really fair to blame the computer. It is really doing only what humans ask.

In other instances the computer is a godsend. Word processing may not be very exciting. Yet it is clearly a boon to companies that have computerized their mailing lists. In research laboratories computers have compressed into days tedious work that once took years. Tracking defective genes and other genes that pass on certain inherited disorders is an example of work carried out here and elsewhere. The human genome project now underway would have taken millennia without the computer. With it scientists hope to have constructed a complete human genetic map well within the lifetime of most Americans.

Far more prosaic is the computer use described in the lead article of this issue. But in fact the article is really about two different uses of the computer. Before computers, diagnostic radiology consisted of relatively simple images such as the conventional X ray or of coronary angiography, a sort of movie of blood coursing through the arteries.

Such simplicity changed when innovators began marrying radiation to the computer. First computed tomography (CT) made it possible to look at slices of the brain and other parts of the body. Before CT the only way of deriving similar information was at autopsy. PET scanning (Positron Emission Tomography) goes beyond the anatomic to show how parts of the body are functioning biochemically. MRI (Magnetic Resonance Imaging) uses magnets rather than radiation, but it is as dependent on the computer as CT and PET.

So important have CT and MRI become that in many instances it would be considered malpractice not to use them. Needless to say there has been an explosion of image use in hospitals. As a result of this use and the sheer number of records, the MGH has ultimately needed to store records of former patients in a warehouse several miles away. The article referred to explains how the computer plus use of fiberoptic cable can reduce the transit time for images from the warehouse to an MGH office from hours to six seconds. Here then you have images made by one computer technology relayed almost instantaneously by another. Remarkable? Yes. Especially since the age of the computer has barely emerged from infancy.

# *Pain in Children*

*(Continued from Page 1)*

found that nerve tracts associated with pain sensation in the spinal cord and brain stem are completely myelinated up to a midportion of the brain (the thalamus) by 30 weeks of gestation.

*Evidence has even been gathered that as early as seven weeks after conception, the mouth of the fetus has sensation.*

Some practitioners associate a specific level of pain — mild, moderate, or severe — with a specific affliction, but Dr. Lebel-Schwartz said there is no physiologic justification for that.

"Children who have rheumatoid arthritis, for example, may experience exquisite pain in their joints while other youngsters with the same disorder are much less affected and remain quite active," said the MGH physician, who is also Assistant Director for Neurology of the pain program at the Spaulding Rehabilitation Hospital, a major MGH affiliate.

Another contention that is only partially true: Children process (metabolize) pain-relieving drugs differently than adults. Children may be exquisitely sensitive to narcotics, the argument goes, and therefore smaller doses may be justified.

It is true, said Dr. Lebel-Schwartz, that babies under one month of age metabolize narcotics differently and that a lower dose for them may be necessary. But after a month of age, she said, children metabolize narcotics in very similar fashion as adults.

Just as an adult's sensitivity to pain can vary from that of another adult, so can the

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PHOTOGRAPHS: Page 1, The Oucher, developed and copyrighted by Judith E. Beyer, RN, Ph.D., 1983; pages 4, 5, 6, 7, 8, Myron Daniels. DRAWING: Page 3, from Advances in Pain Research and Therapy, 1985, reproduced with permission from Raven Press, New York.

sensitivity in children be different. Their reactions to painful stimuli appear to be contingent upon their level of cognitive, social, and emotional development. From infancy to 2 years of age, reactions to pain are reflected in behavioral changes, such as screaming, crying, flushing, sweating, vomiting, or rapid breathing.

These behaviors still apply between the ages of 2 and 7. The children do not yet link pain with an illness. Instead, they may fantasize that they have been naughty and that the pain is a punishment. It is important to reassure children that their pain has nothing to do with their behavior.

Children between 7 and 9 exhibit less overt distress. They understand that even if they must undergo a painful treatment, like an injection, it will probably shorten the overall duration of their discomfort. They don't realize, however, why the needle is important to their care.

From age 11 into adulthood there is a greater understanding of the mechanisms of pain and ways of coping with it. Children as young as 11 are able to undertake such coping techniques as imagery, relaxation, and biofeedback.

Dr. Lebel-Schwartz said, however, that drugs are the cornerstone of therapy for both acute and chronic pain in children.

If the pain stems from a nonmalignant condition, such as rheumatoid arthritis or sickle cell anemia, a nonnarcotic agent is usually tried initially to relieve pain. If inadequate, the drug can be combined with a weak narcotic, such as acetaminophen (Tylenol) with codeine.

Pain from a malignancy may require treatment with a narcotic gradually strengthened to meet the patient's need. This is especially true in instances of chronic, ongoing cancer pain.

Dr. Lebel-Schwartz, who is active in the MGH's Cancer Pain Center, said that taking the weight difference into consideration, the narcotic dosage given to a child with cancer pain may very well be the same as that prescribed for an adult.

A key reason for some centers' undertreating pediatric pain has been an apprehension that children who use potent medicines at a young age will have a higher risk of later becoming addicted to the drugs. Dr. Lebel-Schwartz said there is nothing in the medical literature to substantiate such concerns.

Recent years have seen dramatic advances in the use of narcotics to manage postsurgical pain. At the MGH, patients benefitting from a technique called patient-controlled analgesia (PCA) range as young as 6 years of age.

A special, battery-powered pump containing a syringe filled with morphine is placed at a patient's bedside. A tube (catheter) extends from the pump to the patient's arm. When pain relief is needed, the patient simply presses a button causing the pump to deliver a precalculated dose of the drug intravenously (*MGH News*, October 1988).

Dr. Daniel B. Carr of the MGH's Postoperative Pain Service said that each week between five and ten children are enrolled in the PCA program, both at the MGH and at the nearby, affiliated Shriners Burns Institute. The young patients spend several days on the pump.

Before being accepted for PCA, the children must show that they understand the nature of the program and give assurance of cooperation with the staff.

Another important pain relief delivery system following surgery involves the use of an epidural catheter. This is a thin tube that passes from the surface of the lower back into a space next to the dura, the outermost membrane covering the spinal cord. Drugs delivered through the tube are absorbed through the dura into the spinal cord, thus controlling the pain.

Dr. David Todres, Director of the MGH's Neonatal and Pediatric Intensive Care Units, said that with the epidural catheter "we can much more selectively control pain in the area of an operation."

He explained that when pain relief medicine is given via a muscle or a vein, the drug causes sedation and may also affect blood pressure, breathing, and heart rate. All of this is carefully controlled by the amount of drug administered.

"When we give a pain reliever through an epidural catheter," he said, "we are making sure that the medication acts only around the area of the nerves going to where the operation was performed. While gaining pain relief, the patient is less sedated."

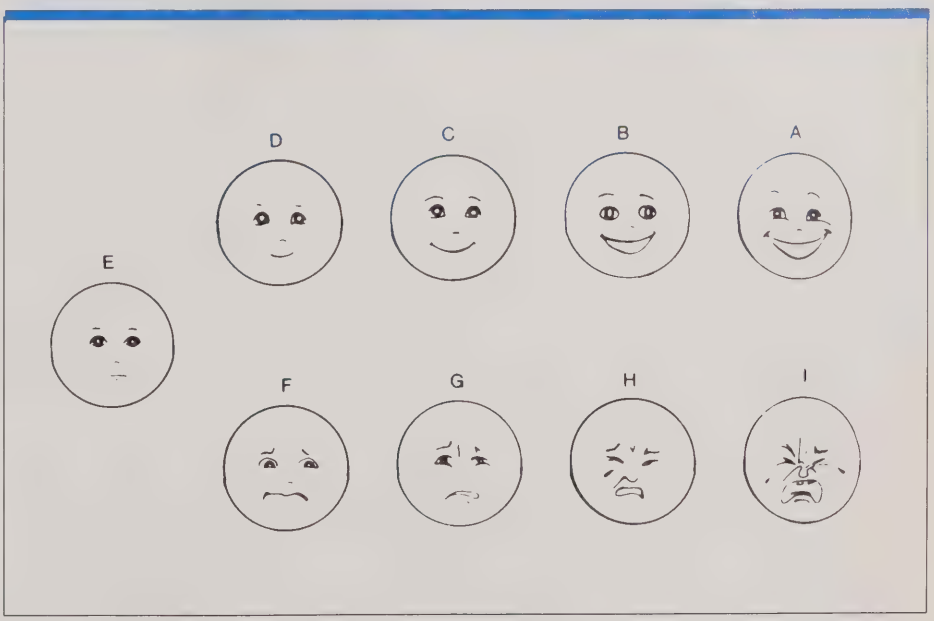
This is important, Dr. Todres said, because after surgery a child should be able to cough deeply to bring up secretions which tend to pool in the lungs and may cause problems related to oxygen levels in the blood. If the child has been very sedated for pain relief, a therapist may not be able to get the best cooperation from the patient for deep breathing exercises.

Dr. James K. Alifimoff, a pediatric anesthetist, (or a member of his team) installs the epidural catheter in the operating room following surgery but before the child awakens. Later Dr. Alifimoff or a colleague visits the patient in an intensive care unit to administer the pain reliever and monitor the child's response to make sure the dosage is appropriate.

"After a child has gone through a painful operative procedure," said Dr. Todres, "we strive to make the recovery as comfortable as possible. When we fail to do that as effectively as we can, then we have really come up short in terms of our commitment as physicians to healing that child."

Dr. Todres' comment is underscored by the words of 17th century English poet John Dryden:

*For all the Happiness*
*Mankind Can Gain,*
*It is not in Pleasure*
*But in Rest from Pain.* ■




*Another facial scale for children to indicate their pain levels. A to D represent varying degrees of positive emotion while F to I display increasing negative feelings. Face E is considered a neutral expression.*

# — Reducing the Wait for Stored Records

*(Continued from Page 1)*
that are linked to a central bank of computers. In addition to being able to recall films from Somerville, the computers have begun to store newer images on optical discs at the main campus.

*These images, most of them collected in the past year and a half, already exceed 263,000. A box only two feet high, one foot wide, and two feet deep can hold hundreds of thousands of medical images.*

*During the first phase of RSTAR's functioning, the job of finding desired films on an optical disc and transmitting them to a work station took just seconds.*

*"In the project's second phase, which we are now entering, we can transmit many times faster than before," said Dr. James H. Thrall, the MGH's Radiologist-in-Chief. "We soon will be able to call up a full chest X ray in under one second."*

In addition to an RSTAR central demonstration facility, the network has stations in areas concerned with skeletal radiology, MRI (magnetic resonance imaging), vascular (blood vessel) radiology, and nuclear medicine. A station was also established in nearby Cambridge to enable engineering support personnel to monitor RSTAR's operations.

In another year, RSTAR will boast 13 work stations. In addition to those on the main campus and in Cambridge and Somerville, stations will be established at the hospital's MR Imaging Center in Charlestown, at the Spaulding Rehabilitation Hospital, a major MGH affiliate in Boston; and at the Burlington center of the Harvard Community Health Plan.

Jaime L. Taaffe, Director of PACS (Picture Archiving and Communications Systems), described some of the important qualities of RSTAR, which is a function of PACS and was developed at the MGH with Dr. Roger A. Bauman, an Associate Radiologist-in-Chief.

In skeletal radiology, said Mr. Taaffe, who is also the Radiology Department's Director of Computing, the task of obtaining bone density measurements from the CT scans of osteoporosis patients used to occupy the full time of a radiologist. Today, RSTAR, equipped with special software, performs that work automatically. It now takes a radiologist only a few minutes twice a week to keep informed about the bone density status of a dozen or more patients.

In addition to displaying still pictures, RSTAR can transform a sequence of images into real time, or motion picture fashion, so that blood flow and the beating of the heart, for example, can be viewed in action and assessed.

RSTAR can be instructed to display an image at any number of MGH work stations at the same time so that physicians, looking at separate screens, can consult.

Mr. Taaffe said that in electronically storing images at the hospital, high priority is being given to films relating to emergency or unscheduled patients. Next, all MR and CT images will be stored on discs. Toward the end of the year, films of patients in some intensive care units will be stored in RSTAR's computers.

"All of the images originating in nuclear medicine during the past year already have been archived," said Mr. Taaffe.

"Ultimately we hope to maintain complete, lifetime records on patients. If an image can be stored electronically, so can a written file, including information on a patient's history, the results of physical exams, and laboratory reports."

Dr. Thrall described the ultimate transfer of all record-keeping operations into the electronic age as essential. The Radiology Department, he said, is generating more data than it can manage using conventional physical means.

The department performs some 350,000 radiologic exams each year, almost 1,000 every day. In addition, physicians check out between 1,000 and 3,000 images daily from the hospital's film library.

Although a staff of 59 film librarians strives to coordinate the movement of patient records, there is no guarantee that every one being borrowed will be returned. RSTAR assures not only that it will prevent such losses but also that images will be available to as many doctors who want them.

In a related activity, the MGH has joined in a three-year trial with NYNEX, its New England Telephone subsidiary, and three other Boston hospitals to develop a high-tech telecommunications service that will link all of the hospitals.

While the MGH contributes its expertise in radiologic record keeping, Children's Hospital, the New England Medical Center, and the Brigham and Women's Hospital will look at other potential applications for electronic data transmission.

While the hospitals develop software on the users' end, NYNEX will focus on the fiberoptic network necessary to connect the users. Because such cable has a higher band width than others, it has a greater capacity to transmit large amounts of information.

Dr. Thrall said he found it a little ironic that computer use in business and industry has outpaced medical applications of these electronic wonders.

At the MGH, RSTAR is already serving as a prime example of the benefits available to patient care from computer technology.

*"When I look at the future of hospitals and health care systems," Dr. Thrall said, "one of the distinguishing features is going to be how well they handle data."* ■

***Left:*** *Jaime Taaffe, who heads the MGH's PACS program, loads an RSTAR computer with an optical disc capable of storing tens of thousands of radiologic images.*

***Below:*** *Dr. Daniel Rosenthal, Chief of the Skeletal Radiology Division, notes bone density measurements provided by an RSTAR computer from CT studies of an osteoporosis patient.*

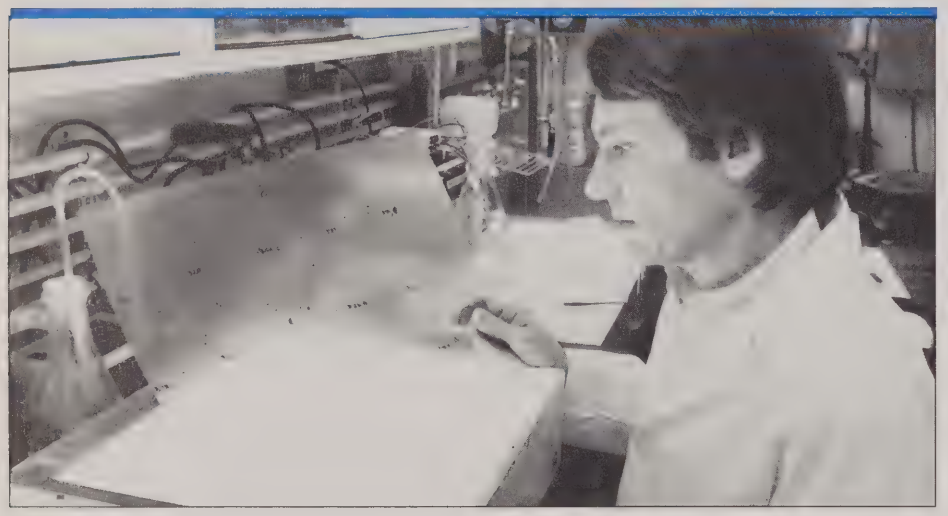
***Right:*** *At the MGH's medical records warehouse in a Boston suburb, a room reserved for radiologic files covers half an acre.*

# Looking for Ways to Access the Brain

SOME YEARS AGO, as part of an experiment, a scientist injected a harmless dye into a laboratory animal to turn its tissue blue.

The stain did its job throughout the animal's body except for one place, the brain. The brain remained pink.

What kept the dye out? New probes of brain structure and function stirred by this laboratory phenomenon led to a realization that the brain not only controls the body but is also equipped with a set of unique defenses.



*Dr. James Nathanson examines a film showing genes from hormone receptors in the blood brain barrier.*

These became known as the blood brain barrier and the blood-CSF (cerebrospinal fluid) barrier. Their role: to provide the brain with a controlled environment and to exclude unwanted and potentially harmful substances.

What makes this exclusion possible in one respect is that very small blood vessels (capillaries) in the blood brain barrier have a special makeup. While those elsewhere in the body contain tiny holes through which substances can cross from the blood into tissue, the capillaries in the blood brain barrier have no holes. Also, the cells (endothelial) lining these capillaries are tightly joined.

In the blood-CSF barrier, capillaries making up loops of blood vessels do have holes, but they are covered by a single layer of cells (epithelial) which comprises the barrier.

The barriers are selective about what gets through to the brain. For example, the entry of glucose, a sugar essential for energy, is actually facilitated while the entry of the amino acid derivative, tyramine, is largely prevented.

Tyramine is found in such dietary items as chocolate, cheese, herring, and red wine. Because of a similarity with the stress hormones epinephrine and norepinephrine, tyramine in excess amounts can interfere with the way in which nerve cells and those hormones interact. If too much tyramine got into the brain, it might disrupt the transmission of nerve-to-nerve chemical impulses and affect a person's behavior. So the brain barriers keep tyramine out.

The brain also likes to be isolated immunologically, and it therefore excludes antibodies as well as many lymphocytes (defensive white blood cells). One reason is that the brain may produce unique substances which would trigger the body's immune system to attack those substances and even the brain itself.

In their protective role, however, the blood brain and blood-CSF barriers also keep away drugs which could otherwise fight brain maladies, such as Parkinson's disease, Alzheimer's disease, certain infections, and tumors.

In the MGH's Neuropharmacology Research Laboratory, a team directed by Dr. James A. Nathanson, has been trying to develop drugs capable of regulating the barriers and treating brain disease.

In particular, Dr. Nathanson has focused on the factors which control the normal movement of fluid from the blood into the brain. This movement occurs at the brain's capillaries and particularly in the kidney-like choroid plexus, situated within the CSF-filled cavities (ventricles) of the brain. The choroid plexus plays a key role in producing the CSF.

Fluid balance often goes awry following head trauma or stroke, causing surrounding tissue to swell and increase pressure within the brain. Sometimes a child is born with an inadequate drainage system for the brain's fluid, a condition called hydrocephalus.

In addition to studying the brain barrier tissues themselves, Dr. Nathanson has used the eye as a model of the brain. The eye has an organ called the ciliary process which secretes a fluid similar to CSF and has a thin, soft (membranous) structure almost identical to that of the choroid plexus. The ciliary process keeps the eye inflated and round and also delivers nutrition to the lens and cornea.

When fluid drainage in the eye fails, the eye's pressure rises, leading to glaucoma. If the pressure reaches sufficiently high levels, nerve cells in the retina die, and blindness results.

In studies underwritten by the National Eye Institute and Nova Pharmaceuticals, Dr. Nathanson found that a heart drug used for more than a century could trigger a chemical reaction that decreases pressure within the eye. Drops of nitroglycerin, a medicine normally prescribed for relief of chest pains, reduced pressure in the eyes of both rabbits and monkeys.

"The dosage we gave was very low," the MGH neurologist said. "In fact, it was so small that the drug had no effect on any other part of the body."

Is nitroglycerin the answer to bringing down pressure in the brain caused by fluid imbalance?

"A great advantage with this drug and others like it is that they pass right through the brain barriers," Dr. Nathanson said. "But while measuring nitroglycerin's effect on the eye is a simple process, monitoring what the drug might do in the brain is complicated. We have not yet tried nitroglycerin on the brain."

Clearly, he said, improved methods are needed to reduce abnormally high brain pressures. At present, neurosurgeons commonly turn to a drug like mannitol which can draw fluid from the brain but which dehydrates the rest of the body at the same time.

"Even in the best of circumstances," Dr. Nathanson said, "it has not always been possible to control pressure in the brain."

As part of his brain research effort, the MGH specialist is also trying to determine if the brain barriers are involved in immunological communication.

The cells making up the barriers are unique in that one side of each cell faces the blood and the other side faces the CSF. It's like a Berlin Wall with the layer of cells strung along the top, point-

ing toward both East and West Berlin.

In collaborative studies with Dr. Linda Chun, also of the MGH Neurology Department, Dr. Nathanson injected virus-size particles into brain tissue and found 24 hours later that the cells (epithelial) covering the choroid plexus had become loaded with these particles.

"In gobbling up the particles from the CSF, the barrier cells acted very much like macrophage, or scavenger, cells," Dr. Nathanson said.

In tissue culture, he said, the epithelial cells present their foreign particles to the immune system's lymphocytes and can activate them. Once activated, the lymphocytes are believed to be able to cross the brain barriers.

Dr. Nathanson, who is also Associate Professor of Neurology at Harvard Medical School, said he is looking for a drug that will help in the activation of lymphocytes and at the same time control the immunological response in the choroid plexus.

In multiple sclerosis, for example, the immune system is too active and breaks down a protective sheath of myelin around nerves. If the barrier system is involved, can the epithelial cells be turned off to make the activation of lymphocytes less likely? This might alleviate MS.

In other situations, such as in combatting brain infections, one might want to "soup up" the immunity. Is there a proper drug for that?

Suggestions for manipulating, tricking, or avoiding the brain barriers have stirred much interest among researchers and led to some developments.

People, for instance, often take an antihistamine for a cold or allergy and, because the drug reaches the brain, sleepiness has become a side effect of the medication. A newly available form of antihistamine treats the cold or allergy without causing sleepiness. The redesigned structure of the drug prevents it from crossing the brain barriers.

But what about *wanting* to get a drug into the brain? A hormone, cholecystokinin (CCK), has an ability to alter one's appetite and thus appears to offer a way to counter obesity caused by overeating. But CCK cannot reach the brain, the site of appetite control. CCK is a polypeptide (made up of linked amino acids) which is too big to penetrate the brain barriers. Can drugs be developed which are not peptides but which can mimic CCK just the same?

"Some drugs which we'd like to get into the brain are very difficult to modify," said Dr. Nathanson. "They're either too large, electrically charged, or based on proteins. Our work has shown, however, that the barriers' cells contain receptors that can respond to certain hormones from either the blood or the brain. Maybe one solution to what we're trying to do lies in using those hormones to manipulate the barriers." ■

# *Drug May Give Long Relief From Bulimia*

ONE OF MEDICINE'S newest drugs to overcome depression is demonstrating that its capabilities don't stop there.

The federal government licensed fluoxetine as an antidepressant a year and a half ago, but researchers were allowed to try it against other disorders on an investigational basis.

In the short time of its availability, fluoxetine has also been shown effective against obsessive-compulsive disorder which strikes five million Americans (*MGH News*, October 1989), and studies indicate that the drug can offer sustained benefits in the treatment of bulimia.

Bulimics, mainly young women, gorge themselves on food and then, feeling pangs of shame and guilt, seek quick relief. They empty their systems by either gulping laxatives or inducing vomiting. Soon, however, driven in part by depression and low self-esteem, they return to binging and purging (*MGH News*, October 1981).

Last year, a trial use of fluoxetine among more than 400 bulimic patients at 14 centers, including the MGH, led to an approximately 75 percent reduction in binging and purging episodes during the first 6 to 8 weeks of treatment.

The question then arose: If such patients remained on the drug, would the beneficial response continue? At the MGH, a team from the Psychiatry Service set out to learn the answer. The team consisted of Drs. Maurizio Fava, David B. Herzog, Paul Hamburg, Helen Riess, and Jerrold F. Rosenbaum, and a research associate, Stuart Anfang.

The group studied 19 MGH outpatients (18 women and 1 man) who had demonstrated significant improvement during the first 6 to 8 weeks of treatment with fluoxetine and had continued the drug for an average of 10 months.

Writing recently in the *Annals of Clinical Psychiatry*, the MGH team reported that the study participants tended to maintain the improvement originally noted in the 14-center trial. Dr. Fava of the Clinical Psychopharmacology Unit, who was the paper's principal author, wrote that the average frequency of binges and purges was about 6 a week at the start of treatment and after 10 months had decreased to 1.4 per week.

Dr. Herzog, Director of the MGH's Eating Disorders Unit, said in an interview that it is too early to know if fluoxetine is more effective against bulimia than other medications, but, he said, fluoxetine does appear to be better tolerated.

"One of the best studied drugs to date for bulimia has been the MAO [monoamine oxidase] inhibitor phenelzine," said Dr. Herzog, who is a pediatrician as well as a child and adult psychiatrist. "But while phenelzine was shown to be effective in reducing instances of binging and purging, patients could not stay on that drug because of side effects, including dizziness."

Dr. Fava also told *MGH News* that

*(Concluded on Page 8)*

*Drs. Maurizio Fava, left, and David Herzog discuss details of new bulimia research.*

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# *Can a Return of Bulimia Be Predicted?*

*(Concluded from Page 7)*

when tricyclic antidepressants are used to treat bulimia common side effects are constipation and weight gain. Since bulimics are already preoccupied with their body shape and weight, long-term treatment with these drugs is sometimes not possible because of the unacceptable side effects.

Fluoxetine does not cause constipation and does not seem to induce weight gain.

The MGH trial also showed that the improvement of bulimic patients while under fluoxetine could be maintained at roughly half the 60 milligram (mg) a day dosage used in the multicenter study.

"We started treatment at a low dose of 20 milligrams, watched the patient's response, and then increased the dosage if the response called for it," Dr. Herzog said. "Only a few patients needed as much as 60 milligrams."

In the multicenter study, the patients relied only on the drug treatment. In the subsequent longer-term study at the MGH, patients received psychotherapy as well as fluoxetine.

Drs. Herzog and Fava are now engaged in a new year-long study of 20 bulimic patients. This time, in addition to evaluating the effects of fluoxetine, they hope to learn whether they can detect any physiologic or psychologic predictors of an impending relapse if symptoms of the disorder recur in an individual.

"We're looking for certain neurochemical derangements that may be associated with bulimia," Dr. Fava said.

Such patients often exhibit subnormal levels in the brain of a signal carrier called serotonin. Deficiencies of this substance have been linked to depression and anxiety and, it is thought, may also figure in the bulimic's desire to eat more and more. Fluoxetine tends to increase serotonin levels.

Dr. Fava said that researchers in this field hope to learn whether any neurochemical changes (including serotonin) found in bulimics resulted from their behavior or actually were involved in development of the disorder. If the latter is true, then it might be possible to devise ways to control the changes and thus effectively treat the illness.

The role of neurochemical changes in another serious eating disorder, anorexia nervosa, is also under intense study. While bulimics binge and purge, anorectics, obsessed with the idea that thin is beautiful, go on virtual starvation diets. The knowledge that they might die from this behavior fails to alter their course.

The extreme dieting appears to lower levels in the brain of the stress hormone norepinephrine which normally increases in the presence of anxiety. Thus, whenever anxiety seems to be on the rise, the anorectic finds relief by shunning food.

Still another neurochemical alteration reinforces support for the severe dieting. The avoidance of food leads to a rise in the brain's levels of chemicals called opioids which produce a false sense of euphoria or well-being.

Dr. Herzog said that anorexia, unlike bulimia, is not consistently responsive to drug treatment. Even if an effective drug were available, many anorectics would find it difficult to accept medication.

"Often these patients don't see that they have a problem," said Dr. Herzog. "They are reluctant to put anything in their mouths, and, on top of everything, they are very sensitive to side effects from drugs."

In the MGH Eating Disorders Unit (the first outpatient evaluation and treatment center of its kind in New England when established in 1981), bulimics account for about 80 percent of the patients. The remainder have anorexia.

"Estimates of the number of people in the general population who have bulimia vary tremendously," Dr. Herzog said. "While 10 or 12 percent in one group may be seen engaged in bulimic behavior, only 2 or 3 percent actually meet psychiatry's diagnostic criteria for the disorder."

The Diagnostic and Statistical Manual of Mental Disorders (Third Edition Revised) describes the following as characteristic of bulimia:

Recurrent episodes of binge eating occurring at least twice a week for three months, lack of control over eating behavior during the binges, persistent overconcern with body shape and weight, and the use of self-induced vomiting, laxatives, diuretics, dieting, or vigorous exercise to prevent weight gain.

Whatever the number of bulimics or anorectics in this country, Dr. Herzog said:

"It is a rare person today who hasn't encountered someone struggling with an eating disorder." ■

*Refrigerator revisited ... People with bulimia cannot seem to eat enough.*

MGH News

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# New Liver-Biliary-Pancreas Center

FIFTEEN YEARS AGO, a patient suffering from gallstones or from a narrowing or blockage of the common bile duct located between the liver and gallbladder faced major surgery.

Today, that same patient has a wide range of treatment options, both surgical and nonsurgical. The newest of these is a revolutionary technique that uses a television camera and requires only tiny abdominal incisions to remove a diseased gallbladder.

In some cases, the problem can instead be corrected through a lighted tube called an endoscope. The tube is inserted through the mouth and intestines, allowing doctors to examine the bile duct. Through this lighted tube doctors can insert a smaller tube (catheter) or other specially adapted instruments and perform a number of different procedures, depending on the nature of the problem.

If, for instance, a stone is causing the blockage, the doctor can either remove it, fragment it, or open up the lower end of the bile duct to allow the stone to pass. If there is no stone, but rather a narrowing of the duct, the doctor can enlarge it.

Another possible option is to use interventional radiology techniques. In this approach, the radiologist, using a local anesthetic and guided by the three-dimensional imaging techniques of ultrasound and fluoroscopy, enters the *(Continued on Page 2)*

*Workmen help lower the hospital's new cyclotron into place. The cyclotron produces the radioactive isotopes used in the PET scanning procedure.*

# *Body's Secrets Revealed With New Imaging Machine*

AN IMAGING DEVICE THAT assesses changes in bodily function has been installed at the MGH to complement CT (computed tomography) and MRI (magnetic resonance imaging) in diagnosing and evaluating disease.

For the last l0 years, MGH specialists in neuroradiology, nuclear medicine, and physics have used positron emission tomography (PET) to study the brain.

While other techniques showed the brain's anatomy or "what was there," PET revealed the status of blood flow and physiological processes, or "what was going on" (MGH News, April 1980).

The instrument newly installed at the MGH is another PET scanner but one capable of studying physiologic function anywhere in the body.

To better exploit the advanced technique, the hospital has installed a new and more modern cyclotron, a device that makes chemicals briefly radioactive for use in the body during PET scanning.

Since the positron emitting isotopes are active for very short periods, they must be produced by an on-site cyclotron.

A physicist in the new program, Nathaniel M. Alpert, Ph.D., said that PET's ability to measure the rates of many biochemical processes, often referred to as metabolism, has important implications for improved diagnosis and treatment. For example, PET can be used to map the three-dimensional distribution of glucose metabolism in the heart.

"A CT scan of the brain of a dead person is indistinguishable from a CT scan of a live brain," he said. "Such scans only show anatomy based on a body's physical composition. PET, however, can differentiate between a brain that is dead and one that is alive."

Although the MGH's Director of Physics Research, Gordon L. Brownell, Ph.D., launched positron imaging studies at the hospital as far back as 1952, and *(Concluded on Page 6)*

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EDITORIAL

# A Man Who Listened

HOWARD ULFELDER spoke eight languages, all of them softly. He was a gentleman and a gentle man. Yet his voice carried around the world. As when the late Dr. Langdon Parsons and he wrote a classic textbook on An Atlas of Pelvic Operations. That text is still used in a number of countries. And many of the young gynecologists he trained are practicing around the United States and the world, passing on to others the knowledge and skills Dr. Ulfelder taught them.

When he spoke, he conveyed ideas precisely. That gave him more time to listen to others - to really listen. Listening is a trait few of us cultivate in our egocentric society. We pretend to listen, but many of us wait impatiently for the first opportunity to express our own thoughts. If that chance comes too slowly, we interrupt, or we seek a way to deflect the conversation to our own direction.

Good listeners tend to make good diagnosticians. Sometimes a patient will drop a telltale clue as when the mother of a patient with vaginal cancer told Dr. Ulfelder of taking hormones while pregnant with her daughter. That was many years ago, and now the daughter had grown to be a young woman with a rare type of vaginal cancer, adenocarcinoma. Could the hormones have somehow caused the cancer so many years later? Dr. Ulfelder listened. And he did not dismiss the notion because it came from a lay person. With two of his MGH colleagues, Drs. Arthur L. Herbst and the late David C. Poskanzer, he began the study which was to demonstrate that the hormone DES was indeed the cause of the cancer so many years after being ingested. Hundreds of thousands-perhaps millions-of American women had taken the drug to preserve difficult pregnancies. Though the mothers were doing what their physicians had in good faith prescribed, many would feel guilty. There could have been panic. That there was not is a credit to all three MGH physicians. As Chief of Gynecology and the most senior among them, it was Howard Ulfelder's soft but authoritative voice that set the tone. It was a day in 1971 that he called the hospital's public affairs director to his gynecology office and revealed the results of the DES study. The paper was to be published several weeks later in the *New England Journal of Medicine*. The news media will call this a time bomb, he said, and terrify hundreds of thousands of mothers and daughters. You have to do everything you can to prevent sensationalism.

The all-important first reports on the day the Journal article was published avoided sensationalism. Even the follow-up news media accounts over the coming years tended to be restrained, pointing out the tiny percentage of at risk women likely to develop cancer from prenatal exposure to DES. The soft, self-assured, kindly voice of Howard Ulfelder kept the public affairs director on a mission to moderate the news media.

Howard Ulfelder died this spring, a victim of Parkinson's disease. He was 78. His accomplishments were much more profound and diversified than this sketch indicates. Had he done nothing more, however, than inspire the cautious approach to telling the story of DES, that would have been achievement enough. ■

## — *Liver Center*

*(Continued from Page 1)*

bile duct by puncturing the liver with needles.

As in endoscopy, a small catheter or other device is inserted into the bile duct, allowing the doctor to perform different procedures. A stricture, for example, can be dilated with a small balloon; a stone can be removed with a little wire basket.

"The same thing the endoscope can do from below, we do from above," said Dr. Peter R. Mueller, Chief of GI Radiology. "Often, we work as a team in difficult cases and do them together."

In other instances, however, neither of these techniques is appropriate. In those patients, surgical reconstruction of the bile duct may be the best course.

Over the last several years, new advances in diagnosis and treatment have greatly transformed the care of liver, biliary and pancreatic disease. Many new techniques (some pioneered here) have been developed. Today, both doctor and patient have a wide array of drug and surgical options and combinations to choose from.

At the Massachusetts General Hospital, specialists from several different departments are able to perform the full spectrum of these treatments for the complete range of disorders affecting these organs.

In an effort to pull all of these specialists and treatments at the hospital under

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PHOTOGRAPHS; Page 1, Courtesy of Cyclotron Laboratory, MGH; Pages 3, 6, Linda Goodspeed; Pages 4, 5, Kennetha Bigham, Myron Daniels, Linda Goodspeed, Bill Miles; Page 7, Courtesy of Dr. Jesse Jupiter; Page 8, Michelle Dorlon, Orthopaedic Media Department, MGH.

one umbrella, physicians from gastroenterology (GI) and gastrointestinal surgery, transplantation surgery, GI radiology, oncology, angiography and pathology have now formed a Liver-Biliary-Pancreas Center. The purpose of the center is to provide a multispecialty resource for patients with complex problems of these organs. A centralized computer referral service facilitates access to the MGH and to the center's 62 participating physicians and surgeons.

"We have experts here at the hospital in all disciplines relating to liver, biliary and pancreas disease," said Dr. Jules Dienstag, a liver specialist and member of the executive committee of the new LBP Center.

"Often patients who come in with these problems have complicated issues that require interdisciplinary input. Until now, we've had no formal way of channeling that input. The idea of the center is to bring together all of the various experts to decide for each patient what should be the best approach."

The effort to form a Liver-Biliary-Pancreas Center at the MGH has been under way for about two years. Dr. Ronald A. Malt, Chief of GI Surgery, said the effort began as a way to make the hospital's expertise in all aspects of liver, biliary and pancreatic disease more accessible to patients.

"Few other hospitals have the depth and breadth of experience we have in all of these technologies," said Dr. Malt, who is also a professor of surgery at Harvard Medical School.

Within the area of liver disease, available treatments at the center range from antiviral drug therapy (the MGH was the first Boston hospital to use interferon for Hepatitis B and C) to liver transplants.

The MGH performed its first liver transplant in 1968. With the introduction of modern anti-rejection drugs, transplant success rates have risen dramatically. Since 1983, the MGH has carried out 98 liver transplants on individuals ranging in age from seven months to 68 years.

"Sixty percent of all of our liver transplant patients since 1983 are still alive," said A. Benedict Cosimi, Chief of the Transplant Unit. "Our recent one-year survival rate is over 80 percent."

Treatments for gallstones and gallbladder complications include drug and chemical dissolution of the stones, lithotripsy (the crushing of gallstones through focused shock waves), lasers that fragment bile stones lodged in the common bile duct (a procedure developed by the MGH's Wellman Laboratories), endoscopic and radiologic intervention, and surgical removal of the gallbladder (cholecystectomy).

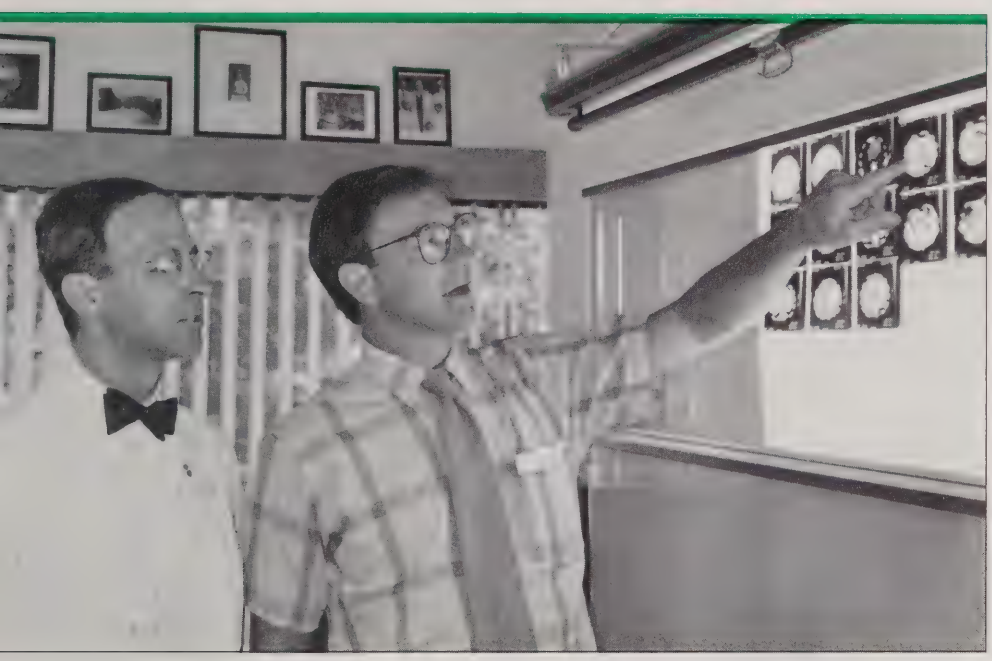
Previously, surgeons removed the gallbladder via a full surgical incision three to six inches long. Over the summer, however, a new surgical technique called laparoscopic cholecystectomy was introduced at the MGH. Instead of making one long incision, surgeons make a tiny hole near the navel and insert a tube with a TV camera into it.

Once they have a clear picture of the abdominal cavity through the laparoscope, the surgeons make three more tiny punctures. Through these holes, they insert tubes and tiny instruments to detach the gallbladder and remove it through one of the incisions.

"Because it's done through smaller entry points, it doesn't seem to bother the patient as much," said Dr. Andrew L. Warshaw, Associate Chief of Surgery.

Patients stay only one night in the hospital and are able to resume full activity with no restrictions within five to seven days.

"It's the most explosive surgical change I've seen," said Dr. Warshaw, who is also a professor of surgery at HMS.



*Dr. Jules Dienstag (left) and Dr. Peter Mueller examine X rays of a patient referred to the Liver-Biliary-Pancreas Center.*

***A national poll of physicians by U.S. News & World Report ranked the MGH's GI Unit the 4th best in the country.***

The MGH carried out its first one on June 4. Since then surgeons have been doing two to three procedures a week.

Treatments for pancreatic disease offered through the center include intraoperative radiation for pancreatic cancer, and pancreas transplants for diabetes. In the latter cases, the kidney is transplanted at the same time, The MGH, which carried out its first pancreas/kidney transplant in 1986, has performed 36 since then.

"In 75 percent of them, the patients are now insulin-free," said Dr. Cosimi, who is also a professor of surgery at HMS.

Once a week center doctors participate in interdisciplinary rounds. At these meetings, various specialists review X rays and discuss potential treatments for patients referred to the hospital.

While the primary goal of the LBP Center is patient care, the center will also focus on education and research. A regular newsletter, speaker's bureau, interdisciplinary postgraduate courses, and regular in-house teaching rounds will be offered. Research goals will develop as the center matures.

"The whole concept is an attempt to bring the full spectrum of knowledge and available technology to bear on these diseases," said Dr. Daniel K. Podolsky, Chief of the GI Unit at the hospital. ■

# New Ellison Building Designed With the Patient in Mind

WHEN THE MGH launched a capital campaign nine years ago to replace or modernize outmoded areas of the hospital, consultants didn't think it could be done.

The goal — to raise $114 million by 1990 — was unprecedented in scope and in the view of fund-raising experts was unattainable. They predicted that it would take a full decade for the MGH to raise just $100 million. And the amount being sought was so much greater. Greater yet when the need for additional facilities and technology boosted the goal to $169 million.

Raising even $169 million by 1990 not only proved possible but the campaign exceeded its goal by more than $6 million!

Mrs. R. Morton Claflin, cochairperson of the campaign, said that three-quarters of the contributions came from individuals, including a legion of grateful former patients. Corporations and foundations provided the balance. Gifts arrived from as far as Asia and Europe.

Even as the contributors responded, the keystone unit of the rebuilding program — a 24-story glass-walled edifice containing a front line of technological know-how for patient care — was rising skyward.

Twenty stories higher than the nearby Bulfinch Building, the MGH's original structure and a National Historic Landmark, the new addition to the hospital's main campus was named the Ellison Building, honoring a prominent Massachusetts family.

A $10 million pledge from the Ellison Foundation of Boston had vaulted the MGH's Capital Campaign past its goal, turning the drive into a resounding success. Dr. J. Robert Buchanan, the hospital's General Director, commented that "the timing could not have been better."

The Ellison Foundation was established by the late Eben Ellison, owner of the Proctor Ellison Company, once a major manufacturer of shoe soles. Mr. Ellison's late children, William Ellison and Mrs. Harriet Ellison Rogers, had supported the MGH for nearly 40 years. Besides the pledge from the foundation, members of the family gave more than $1 million to the campaign.

The Ellison Building, which began receiving patients from outmoded parts of the hospital in early April, is the first of two structures planned on the main MGH campus. The second, 14 stories tall not counting a basement and subbasement, will replace the small-roomed, narrow-corridored Baker Building, a poorly designed inpatient building that dates to 1930 and is no longer adequate for patient care needs.

The second new structure will fill in an open courtyard as well as occupy the Baker site. The two new buildings combined will cover about 23,000 square feet.

With bigger rooms and corridors, both new buildings will facilitate the use of the latest and best high technology. At the same time, larger rooms will in part cause the eventual reduction in the hospital's bed capacity, from the present 1,081 to 977.

Work to tear down the Baker Building, nestled in the center of the campus, is expected to begin around the first of the year and take about six months. Foundation work for the second new building will follow.

Once the second one, as yet unnamed, is completed, sometime in 1994, workers will begin demolishing the 41-year-old Vincent Burnham Building, which has housed the Vincent Memorial Hospital, the MGH's gynecological division; the Children's Service, and the Joseph P. Kennedy, Jr., Memorial Research Laboratories for Mental Retardation.

Still undetermined is the fate of the Phillips House, the hospital's 1917 private pavilion. One proposal is to remove the upper three floors, leaving the lower ones for administrative operations. Meantime, the Phillips House patients are now in the three upper patient floors of Ellison.

***Clockwise from Upper Left:***
*A mural on one of the pediatric floors of the Ellison Building. A pediatric playroom. A control panel for a patient isolation room. A nurse checks a patient on the cardiac floor. The view from the 22nd floor. A nurse monitors a patient by computer.*

All the patient-care floors will have an isolation room in which room pressure can be changed. Increase the pressure and you keep bacteria and viruses away from a patient who has inadequate ability to fight off infection. Decrease pressure and you keep a patient with a contagious disease from infecting others.

Thirty-two committees that included professionals and nonprofessionals met frequently to develop features coming directly from the experience of employees. Incorporating these ideas into the master planning was the architectural firm of Hoskins Scott Taylor and Partners.

One of the features of the new Ellison Building is that many of its floors interconnect with those of the Gray and White Buildings.

The Ellison Building makes up for much of what was wrong with the poorly designed Baker.

"The basic shape of Ellison is triangular," said Burgess P. Standley, Director of Planning. "Its three sides surround a central core where the nursing station is situated. The nurses not only can see into most rooms, they also have quick access to each."

The Surgical Intensive Care Unit on Ellison 4 reflects major design changes to improve service. In each private room, the patient's bed is situated in the center of the room giving physicians and nurses unobstructed access to the patient from any point.

Next to the bed, a power column extends from floor to ceiling. The column contains an array of outlets. Some are electrical; others supply oxygen or compressed air for the patient. Still others suction matter from the chest, stomach, or windpipe. The column also features equipment to monitor blood pressure, heart rate, and other vital signs. On the ceiling above each ICU bed is an oval track from which intravenous equipment can be suspended to any side of the patient. The track also carries power outlets.

Another unique Ellison feature are the lead-lined rooms on six floors of the building. The rooms accommodate patients receiving radiation treatments. Having these special rooms scattered assures that the same nurses will not be called upon to treat each patient. Thus, there is no danger that personnel entering one of these lead-lined rooms might be overexposed to radiation.

Of special importance in the design of the Ellison Building was its basement kitchen. The building's project director, Charles H. Hall, said that the three MGH kitchens were decommissioned so that the Ellison kitchen could take over the task of feeding the entire hospital.

"Between 10,000 and 13,000 meals a day are prepared in this one area," said Helen Doherty, Director of the Dietary Department. "The meals prepared for patients are cooked only partially, then are chilled to about 42 degrees and sent in stainless steel carts to a galley on each floor. There the food is rethermalized to complete the cooking and is served hot."

One of the main reasons for the new meal preparation method for patients is that when mealtime arrives a patient may be away from a floor for a test or other procedure. The new food system assures a hot meal whenever the patient is ready for it. And with one main kitchen instead of three the system is saving money.

One important mechanical feature of the Ellison is a huge multi-elevator shaft for the high-speed delivery of supplies.

"Management, for example, can carry supplies not only to the eighth floor of Ellison," said Mr. Hall, "but also in the same trip to the eighth floors of Bigelow and White. When the second building is complete, the same delivery can include the eighth floor of that structure.

"For the first time, there will be a capability of delivering to four nursing units with just one stop. There is great hope that this will lead to substantial economies."

Funds raised in the Capital Campaign must be stretched far. In addition to the rebuilding program to improve patient care, the money helped finance construction of new research laboratories and endowed scholarships and faculty support at the MGH Institute of Health Professions, which offers master's degrees in nursing, physical therapy, and dietetics.

Another major expenditure was to renovate and modernize existing inpatient buildings that lend themselves to updating. For the White Building, renovation transformed the patient floors into handsome interiors and at a fraction of the cost of new structures.

Before the Capital Campaign could get under way in 1981, the hospital had to establish its Ambulatory Care Center (ACC).

"Outpatients used to go to a variety of buildings for one procedure or another," said Mr. Standley, the Planning Director. "The hospital's main thrust at the time was to consolidate all outpatient activities into a single big structure.

"The building of the Wang Ambulatory Care Center, financed in part by a $4 million contribution by the industrialist, Dr. An Wang, and his family, was a great accomplishment."

The Wang ACC now records more than 490,000 outpatient visits and 8,300 day surgery procedures each year.

*John A. Correia, Ph.D., a leader of the PET team, readies a patient for a chest scan.*

# — PET Scans Reveal Body's Secrets

*(Concluded from Page 1)*

the hospital had a cyclotron as long ago as 1968, PET's use in patient care has taken much longer than its research counterparts because of the technology's complexity.

CT scanners first appeared in 1972, and the following year the MGH became only the second institution in North America to have the device.

"They filled a void immediately," said John A. Correia, Ph.D., another physicist-member of the hospital's PET team. "They represented a further improvement on something better. In the same sense, MRI popped right out of the laboratory and into the clinic.

"PET is much more complex than CT, and the information measured is more subtle. There was not an immediate, obvious application for PET. It's been essentially a research tool."

The complexity of the technology has also made it expensive. The need for a cyclotron as well as a scanner has limited PET's availability to only about 100 research centers worldwide. At the MGH, the new cyclotron and PET body scanner cost nearly $5 million and took almost a year to install.

Dr. H. William Strauss, Chief of Nuclear Medicine at the MGH, called the hospital's financial commitment to PET a "major step forward" in helping to bring the technology out of the lab and into the clinic. He credited Radiologist-in-Chief James H. Thrall with spearheading the effort that, Dr. Strauss said, will make the MGH one of the leading PET centers in the world.

"Thanks to Dr. Thrall, we've got the foundation," he said. "Now all we have to do is build the house around it."

Dr. Strauss said patient care will be the primary focus of the two new machines. "No doubt we intend to pursue research objectives, but we have a combined use in mind," he said. "Our goal is to devote about 50 to 75 percent of the machines' time to patient care. The rest will be taken up with research time that will ultimately make its importance in patient care even greater."

The hospital has already applied for additional research funds from a number of sources, including the National Institutes of Health, the Department of Energy, and several drug and pharmaceutical companies.

Dr. Alpert said PET will be very useful in evaluating new drugs. "Any new drug could potentially be evaluated with PET," he said. "It would be very useful in evaluating how a new drug affects the body's metabolic systems."

While support for the research goals of the PET project appears sound, Dr. Strauss admitted that finding support for patient use of the scanner is more of a problem.

Currently, PET is still considered an experimental procedure. There is no universal third party reimbursement for the test. Dr. Strauss said a nationwide move is under way to gain insurance coverage for PET scans and noted that a few private insurers have already started to pay for them.

"There is pressure building for PET reimbursement just as there was for MRI reimbursement," he said. "I think the path will be very similar."

Initially, however, third party reimbursement will not be an issue with the MGH scanner since the hospital plans to treat patients at no charge during the first few months of the system's operation.

Strauss said doctors will use the PET scan in four primary applications. These include, epilepsy, tumor recurrence, determination of how much of the heart survives a heart attack, blood flow to the heart.

In all four, research has shown PET to be particularly effective. For instance, PET can pinpoint with great accuracy the sites of a kind of epilepsy (focal), differentiate scar tissue from recurrent tumor, and detect coronary artery disease.

"The applications for patient care are huge," said Dr. Strauss.

A PET scan is painless and takes an average of 30 to 60 minutes, depending on what is being measured. The scanner itself looks much like a CT scanner, and the procedure is similar. As in a CT scan, for accurate results, the patient must lie motionless in the machine. Radiation exposure is similar to an abdominal X ray.

Although PET will help doctors make more accurate diagnoses, Dr. Strauss said that is not its ultimate role.

"I think its actual major use will be in providing assistance in therapeutic planning rather than in making initial diagnoses," he said. "The imaging techniques we already have — CT and MRI — will continue to be the main diagnostic tools because they provide exquisite anatomical resolution and have so much to offer.

"PET's role will be to give us information about metabolic function. The whole idea is to get much more information in order to help us better formulate the treatment. The applications for patient care are very exciting." ■

## *How the Technology Works*

The radioactive isotopes produced in the cyclotron are used to label biologically active compounds such as ammonia, carbon dioxide, oxygen, and glucose, all normally found in humans. Once labeled, a compound is given to the patient.

While accompanying the naturally occurring chemical through the body, each radioactive atom quickly decays and emits a positron, or positive charged particle. The positron interacts rapidly with its anti-particle, a negative charged electron, causing both particles to be annihilated.

This creates two high-energy rays (photons) which the positron camera can detect. The camera can then proceed to form two- or three-dimensional images of the distribution of the labeled compound in the body. ■

# Hand Injuries Challenge Surgeons' Skills

THEY FEEL, grasp, manipulate, caress, communicate, and work as a team.

Through the sensitive touch of their fingers, the blind learn to read by braille. People unable to speak turn to their hands for sign language.

Some hand expressions are recognized universally: the clenched fist conveying anger, the raised palm of peace, two fingers spread in a V for victory, a thumb turned up to signal approval or down to register disapproval, and an extended thumb with fingers curled for hitching rides.

As for speed, some say the hand can be quicker than the eye.

Although the hand is only about one percent of the human body, no other part is more physically versatile. But, also, no other part is more vulnerable.

Composed of nerves, tendons, ligaments, veins, arteries, and skin, as well as bones with joints, each finger can be likened to an entire limb. Nowhere else in the body are so many different interrelated structures packed so closely to the skeleton.

"The gliding structures that so intimately envelope the tubular skeleton of the fingers prove in many cases to be the ultimate determinants of functional outcome following skeletal injury," said Dr. Jesse B. Jupiter of the MGH Orthopaedic Hand Surgery Service.

A world renowned British orthopedic surgeon, Sir John Charnley, recognized this fact years ago when he said that a surgeon's reputation can stand as much in jeopardy from a finger (phalangeal) fracture as from any fracture of the thigh bone (femur), the longest bone in the body.

Because of the compact and complex mechanisms involved, Dr. Jupiter said that the management of injuries to the hand can be considerably more difficult than the treatment of an upper arm or a leg.

"This is due in part," he said, "to the small size of structures in the hand and the requirement for magnification (as with the operating microscope) to identify and treat injured elements.

> *Each year the American hand suffers more than 1.5 million fractures as well as nearly 6 million open wounds.*

"The small bones and joints of the hand demonstrate smaller tolerances for disruption than do those of the knee, hip, or shoulder. To accomplish fine motor skills and precision tasks, the digits must be able to move in synchrony."

Fractures of the tubular bones of the hand represent the most frequent of all skeletal injuries. Each year the American hand suffers more than 1.5 million fractures as well as nearly 6 million open wounds. The impact in terms of missed workdays, lost earnings, and costs to industry is staggering.

*Dr. Jupiter repaired a severe fracture at the base of a thumb in the hand of a urologic surgeon. Only 11 days later, the urologist was operating again.*

Injuries occur to digits at least five times more often than to the main portion of the hand. In most instances, even though the skin may remain intact after an accident, the presence of a finger fracture can be readily noted.

Common clues include crookedness of the finger, discoloration of the skin, limitation of movement, and pain.

"Sometimes when a finger has become deformed," Dr. Jupiter said, "people think of a dislocation instead of a broken bone and try to pull the digit back into place. If a dislocation had occurred, such pulling could pop a bone back into its joint. But if the bone had actually broken, the pulling could fragment or shatter the bone further. At times only an X ray can determine the nature of the injury."

Most bone breaks in the fingers result from a twisting action or a fall, such as in a sports activity, rather than from the cutting, puncturing, or pounding impact of some high-energy machinery. For an estimated 75 percent of broken fingers, the physician can effect a repair without surgery.

In such instances, after the broken bone has been carefully restored to its proper position and been splinted or put into a cast, the mending process usually begins within two weeks. By three weeks the bone will have sufficiently healed to permit removal of its artificial support.

During treatment of a finger fracture, physicians must be careful to protect the soft tissues around the finger. While healing, the hand must be held in flexion, the fingers at a sharp angle from the palm instead of out straight. This prevents tendons and ligaments from stiffening and possibly delaying recovery for up to six months.

"You would hate to win the battle but lose the war by concentrating so much on the skeleton that you ignore the tissue around it," Dr. Jupiter pointed out.

Certain fractures by their very nature tend to be unstable, either rotating or angulating.

Because the finger is such a compact entity, bone surgery can be performed without cutting the skin.

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## —*Hand Injuries Test Surgeons' Skills*

*(Concluded from Page 7)*

Guided by fluoroscopy, surgeons can insert so-called "K" (Kirschner) wires through the skin into the bone to hold it intact and in place.

The hand is immobilized for three weeks, and the wires are then removed. A rehabilitative exercise program follows under the supervision of a hand therapist.

When a fracture is so severe that it also causes serious soft tissue injuries and piercing of the skin or results in a splintering or crushing of the bone, surgical intervention is mandated.

In situations such as these, the surgeons may use tiny screws and/or miniplates to aid in the repair. These not only unite the broken bones but also provide the high quality of skeletal fixation necessary to speed rehabilitation of the injured tissue.

The goal is to resume hand movements as soon as possible. Without therapy for the tendons, the structures that pull the fingers up or down, they might not heal well or become scarred, leading to loss of motion.

Similarly, injured ligaments, which hold the bone joints in place, must be treated to regain strength and stability. Untreated, any injured finger would be weak and painful to use. The long-term prospect would probably be arthritis of the joint.

Dr. Jupiter, who is also Assistant Professor of Orthopaedic Surgery at Harvard Medical School, told of operating on a urologic surgeon who had suffered a very severe fracture at the base of his thumb.

The MGH specialist repaired the fracture with two screws. The patient had motion in the thumb the very next day and only ll days later was able to resume surgical care of his patients.

The thumb is involved in nearly 50 percent of a hand's function. Therefore, particular care should be taken to avoid injury to the thumb.

"It is really what separates man and almost all other life forms," said Dr. Jupiter. "Even though other primates, such as chimpanzees, have thumbs, they are very rudimentary and short. The tip of their thumb cannot be brought to their fingers for the kinds of dexterity of which humans are capable."

***A national poll of physicians by U.S. News & World Report ranked MGH the best hospital in the country for orthopedics.***

*Dr. Jesse Jupiter in the operating room*

People tend to take their hands for granted, exposing them to countless contaminants without the thought that any injury breaking the skin might produce a serious infection.

Before the development of antibiotics, a small injury to a finger accompanied by infection often led to an amputation. Today the quick oral administration of antibiotics guards against that kind of outcome. But even in 1990 tetanus still occurs. Tetanus shots are routinely given in connection with hand wounds where infection might set in.

The specialty of hand care evolved only within the past three decades as the importance of the hand's role in daily life became better appreciated.

An amputated digit once had no prospect of salvage. But today, through microsurgery, doctors are able to report multiple-finger replantations with success rates of better than 90 percent.

(The first successful reattachment of a severed human arm was performed at the MGH in 1962, and in 1981 the first successful replantation of as many as seven severed digits also took place at the MGH.)

Hand care is now directed toward the primary treatment of all injured structures rather than the once standard practice of treating one part, waiting for that to heal, and then treating another part.

"With plates, screws, and better bone techniques," said Dr. Jupiter, "we can quickly stabilize an injured bone to permit other care. We can repair injured tendons in a finger and move that finger immediately. Using microsurgery, we can treat injured blood vessels and nerves.

And where there is soft tissue loss, we can replace that tissue with flaps (sections of skin with underlying fat still attached which can be rotated to cover an adjacent wound and still have its original blood supply)."

No longer is a hand injury looked upon as a condition for which basic care is usually adequate. Said Dr. Jupiter,

"Anyone coming to the MGH today for treatment of a hand injury is triaged right away to physicians particularly knowledgeable about the hand." ■

Massachusetts General Hospital, Boston, Massachusetts

MGH News

Vol. 49 No. 7 October 1990

# Center Takes Team Approach to Brain Disorders

THE MGH is intensifying a campaign against two brain disorders that take thousands of lives each year and leave many other victims permanently handicapped. Spurred by new advances in care, including a soon-to-be installed diagnostic device that is the only one of its kind in the world, the hospital has launched a center to cope with aneurysms and congenital arteriovenous malformations (A.V.M.).

A brain aneurysm is a blood-filled bubble at a weak spot on the wall of an artery. Headaches of unprecedented intensity often signal the presence of the out-pouching. Untreated, an aneurysm is likely to grow, and in time burst with possibly fatal consequences (*MGH News, December 1984 and January-February 1985).*

An A.V.M. is a tangle of embryonic veins and arteries that simply failed to mature. Although mild headaches, seizures, limb weaknesses, or brief memory losses can set in, a person may endure an A.V.M. for years, but the potential for a life-threatening stroke is ever present (*MGH News, June-August 1979).*

Aneurysms far outnumber A.V.M.s and account for a great majority of some 28,000 subarachnoid hemorrhages (S.A.H.) in the United States each year. Almost a third of S.A.H. victims die

*(Continued on Page 4)*

# *Surgeons Perform First MGH Lung Transplantation*

A 51-YEAR-OLD MAN unable to breathe without the aid of an oxygen-support system has become the first recipient of a lung transplantation at the MGH.

Surgeons carried out the procedure using techniques pioneered at the MGH. The patient was the first in Massachusetts with emphysema (an obstructed lung disease) to receive a lung transplant. Emphysema, an irreversible, eventually fatal condition, is the most commonly diagnosed lung disease. Until recently, however, emphysema patients either were not considered for transplants or were thought to need a double lung transplant. The MGH patient received a single lung transplant.

"The fact that we can now do a single lung transplant for emphysema means we'll be able to reach many more people with this operation," said Dr. John C. Wain, Surgical Director of the MGH Lung Transplantation Program. "It brings a lot of hope to people who didn't have too much before."

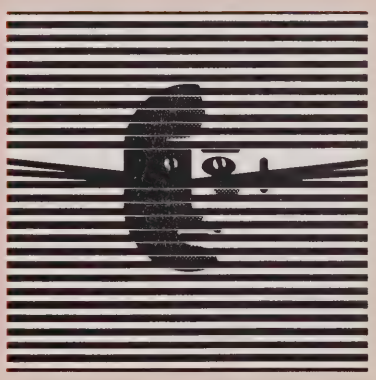
The operation capped off an extraordinary three-day period in August during which three lung transplants were performed in as many days by the new Massachusetts Center for Lung Transplantation (M.C.L.T.).

The M.C.L.T., like its predecessors the Boston Center for Heart Transplantation and the Boston Center for Liver Transplantation, is based on a consortium approach to organ transplants.

Six Boston hospitals and one Worcester hospital make up the consortium. Both the MGH and the Brigham & Women's Hospital are authorized to perform adult lung transplants. Pediatric lung transplants are done at the Children's Hospital.

The remaining four hospitals — New England Deaconess, New England Medical Center, University Hospital, and the University of Massachusetts Medical Center—serve as affiliates and participate in educational and research activities of

*(Continued on Page 2)*



**INSIDE**

**For some, the home becomes a jail.**

***See Page 7.***

## *Another Chance for A Normal Life*

DAVID J. KAMARA, a 51-year-old Dorchester, MA resident who was once a hard-core drug abuser and alcoholic, left the MGH four weeks after receiving his new lung.

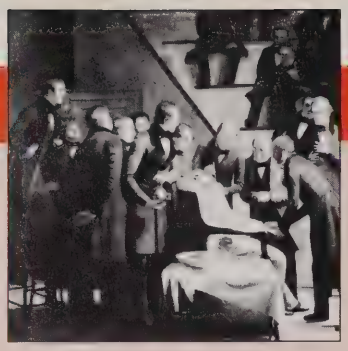
The ex-Marine — the MGH's first lung transplant recipient — had been confined to an oxygen support system since May.

Mr. Kamara credited the support of his family and an alcohol recovery program with helping him first to turn his life around six years ago, and more recently, to decide to try the lung transplant.

A longtime alcoholic and IV drug user

*(Concluded on Page 3)*

EDITORIAL



# Question 3? No!

Massachusetts residents have revived a fraternal organization once known as the Pyramid Club. Only now they call it Citizens for Limited Taxation (C.L.T.). Like the original Pyramid Club, the winners of a successful C.L.T. referendum would be the small number of people at the top of the pyramid. In the long run, however, even the winners would lose.

Question 3 on the November ballot slices state taxes to the 1988 level. Sounds good so far. But for starters, a major segment of our taxes pays for fixed programs—the federal equivalent of Social Security. Do we slash social service programs? How about Medicaid? With a state economy that is already trembling and gasping, should we destruct our schools? At a time when a growing number of our industries need better-educated employees, that course would head the ship of state to the nearest shoal. To avoid the deterioration of education, cities and towns faced with declines in state aid would have to shift the burden to property taxes.

One of the most serious problems with Question 3 is that its passage would downgrade Massachusetts bonds and thus increase the state's cost of borrowing. Like it or not, borrowing is important to the state's cash flow. Making borrowing more difficult and more expensive will achieve the opposite of what voters want: an increase in the cost of running government. Every voter will end up paying more, not less, and in the interim will have to live with a dysfunctional government.

Should we eliminate help for the homeless? That makes as much sense as the movement to give the mentally ill their freedom without providing them with halfway houses and/or some other intermediate support system. Now these unfortunates are free to starve and freeze on the streets. Well, what about Medicaid? Should we limit funding for health care for the poor? Should we really do this at a point when we are faced with an increasing number of jobless?

With America's population aging, there are many more elderly. Elderly, virtually by definition, require more health care. We are not talking about keeping people alive on machines. We are talking about providing care that improves quality of life in the golden years. With the number of AIDS patients increasing, should hospitals stop caring for them because the tax support has plummeted? Or should hospitals close their doors because dwindling support to care for AIDS patients and those on Medicaid leaves hospitals unable to pay their bills?

This publication and the hospital it represents have traditionally eschewed politics. Only when a political course threatens serious impairment of the hospital's 169-year history of serving its patients does the MGH cross that line. A yes vote on Question 3 compromises the ability of perhaps every hospital in the state to serve the sick. ■

## —*Lung Transplant*

*(Continued from Page 1)*

the M.C.L.T. In the future, they may also be authorized to do the procedure.

Because of the remarkable coincidence of having three suitable donor lungs available on successive days, three procedures were carried out in as many days. The Brigham & Women's performed two on August 20 and 21, and the MGH one on August 23.

"It was really very unexpected to have three appropriate donors all at the same time," said Dr. Leo C. Ginns, Medical Director of the MGH Lung Transplantation Program.

In that three-day period, the two hospitals carried out one-fourth of the 12 procedures they expected to do annually.

Although developmental lung transplantation dates to 1963, it has only recently become successful.

During the 1960s and early '70s, surgeons worldwide carried out more than 40 procedures. But only two patients even left the hospital, and interest in the procedure died out.

"The biggest problem with the early transplants was the disruption of the airway," said Dr. Daniel P. Ryan, a pediatric surgeon and member of the MGH Lung Transplant Team.

The disruption was primarily caused by poor healing at the juncture of the lower windpipe and the transplanted lung.

Infection and the risk of rejection of the donor lung posed additional problems for early transplant patients.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To reduce the risk of rejection, doctors put patients on high doses of steroids. But the steroids, while suppressing rejection, increased the risk of infection and contributed to the healing problems in the bronchial area.

The discovery of the drug cyclosporine eased the problem of rejection and meant that steroids could be avoided for the first several post-transplant weeks, thus lowering the risk of infection as well.

But poor healing still remained a problem. Contributing to this difficulty was the fact that the lungs are the only solid organ without a systemic blood supply used for transplantation.

When an organ is removed, its blood supply is interrupted. Unlike other transplanted organs, the lung has two sources of blood — one from the pulmonary artery (the artery that takes blood to the lung to pick up oxygen), and the other from the bronchial arteries (the arteries that take blood to the bronchus, or air passage, that leads to the lung).

"When you divide the two arteries in a lung transplant, you can only reattach the pulmonary arteries," said Dr. Wain, who is also an Associate Professor of Surgery at Harvard Medical School.

"The bronchial arteries are so small you can't really sew them back together."

Because of these problems, surgeons initially found it easier to transplant both the heart and the lungs at the same time.

The first heart and lung transplant, performed in 1981, was followed by others.

Doctors now say that many of those recipients of both organs needed only lungs, but successful transplants of the lung alone awaited the development of new surgical techniques.

Dr. Joel Cooper performed at Toronto General Hospital the first successful lung transplantation of the modern era. Dr. Cooper trained for seven years at the MGH, including a year under the direction of Dr. Hermes C. Grillo, Chief of General Thoracic Surgery. Dr. Cooper is credited with adapting surgical techniques pioneered by Dr. Grillo to make lung transplantation feasible.

One of these techniques involved trimming back the bronchus of the donated lung to reduce the region deprived of a blood supply and facilitate healing.

Another and more important Grillo adaptation that also promoted healing in the bronchial area was the use of the omentum, a membrane from the abdomen.

The long, fatty membrane, which is full of blood vessels, functions on the abdomen to seal any disease, such as a perforated ulcer, that might develop.

Dr. Grillo helped perfect the use of the omentum in thoracic surgery for tumors and during reconstruction of the airway, a procedure pioneered at the MGH.

"Dr. Cooper's contribution was to apply this technique [known as the omentum wrap] to lung transplants," said Dr. Wain.

The omentum is long enough for surgeons to pull it up to the chest cavity (leaving the blood vessels attached to the abdomen) and wrap it around the bronchus. "The omentum does several things," said Dr. Wain. "It seals the area of the anastomosis [junction] so air and bacteria can't leak out. And becauseit has blood vessels in it, it can nourish the blood vessels on the donor lung."

In addition to Dr. Ryan, Dr. Wain was assisted by Dr. Douglas Mathisen.

"The operation was a team effort." said Dr. Wain. "It involved many anesthesiologists, nurses, residents, and surgeons all working together."

Dr. Ginns said the critical postoperative period was also a team effort involving nurses, physical therapists, doctors, pulmonary care specialists, and many others.

"Up until lung transplants, there has been very little we could do for patients with a number of end-stage lung diseases," said Dr. Ginns. "There have been few thera-peutic advances to rival lung transplantation. This operation offers hope for those people with otherwise irreversible end-stage lung disease. They may be restored to a high-quality functional lifestyle. The only limit we face is the availability of suitable donors." ■

## *Another Chance for a Normal Life*

*(Concluded from Page 1)*

and seller, Mr. Kamara tried various treatment programs but always wound up back on the street. The turning point came six years ago this Thanksgiving when he joined a 12-step recovery program.

Following his discharge, Mr. Kamara returned to the hospital daily for the first week for blood and other tests. After that, he came to the hospital three times a week, and eventually will come once a month.

At home, Mr. Kamara was responsible for keeping a daily journal in which he kept track of his weight, temperature, heart rate and lung function. Within hours of the operation, Mr. Kamara's arterial oxygen blood level (the amount of oxygen getting into his bloodstream) had doubled, and his lung volume (the amount of air he could expire in one second) had tripled.

Mr. Kamara was also responsible for taking his own medications, which include cyclosporine and imuran — both immunosuppresants — and prednisone, a steroid. His daily exercise program included a one-mile walk and two 20-minute sessions on a stationary bicycle.

An important part of Mr. Kamara's postoperative therapy is the support group for lung transplant patients that he attends once a week at the MGH. Four other Massachusetts residents have received lung transplants — either in Canada or out-of-state. They meet to discuss their common experiences with each other and with other patients still waiting for lungs. ■

*David J. Kamara, the MGH's first lung transplant patient, is flanked by Drs. John C. Wain (left) and Leo C. Ginns.*

# — Center Takes Team Approach to Brain Disorders

*(Continued from Page 1)*

outright. Another third succumb later or suffer lifelong disabilities.

Each Friday morning at 7, members of the new Brain Aneurysm/A.V.M. Center convene to discuss patients with either condition and to map a course of action for each individual. Dr. Robert M. Crowell, Chief of Cerebrovascular Surgery in the Neurosurgical Service, heads the new brain center.

The Brain Aneurysm/A.V.M. Center soon will be equipped with a multimillion dollar device capable of providing the earliest possible diagnostic information on the two brain conditions.

This fluoroscopic instrument, called a G-Ring because of its configuration, will be employed by Dr. John M. Pile-Spellman, Chief of Interventional Neuroradiology, to show brain blood vessels in real time, or movie-like fashion. The machine, which is produced by Toshiba America Medical Systems, gives the clearest pictures yet available of brain circulation.

CT (computed tomography) continues to be a principal diagnostic tool. Assessing the size and source of a vascular spill by means of a CT scan helps to determine the course of treatment. Dr. J. Philip Kistler, head of the MGH Stroke Service, and Dr. Daryl Gress conduct these studies. Dr. C. Miller Fisher serves as an adviser.

MRI (magnetic resonance imaging) also is prescribed for selected patients when improved definition of vascular anatomy is required. Still another imaging technique, PET (positron emission tomography), can reveal changes in physiologic function during treatment.

*By uniquely having all of these high technologies available, the center hopes to provide patients the best possible chance for outstanding care.*

A new strategy for aneurysm treatment has been adopted at the MGH in the past few years.

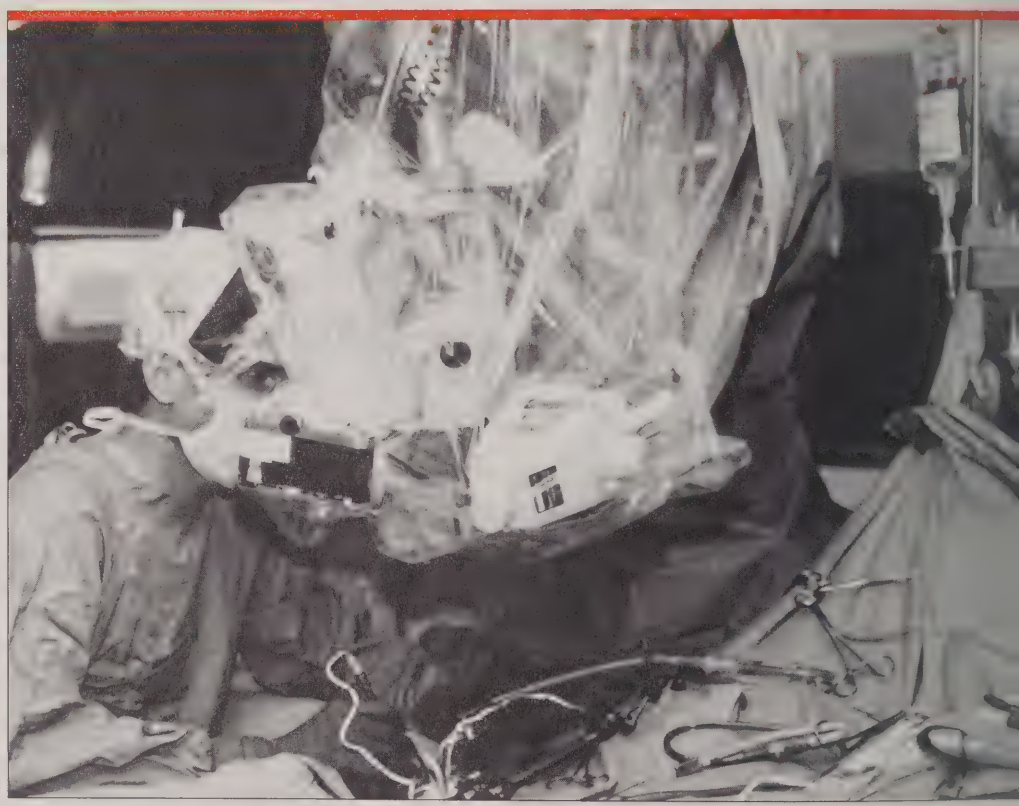
Traditionally, surgeons delayed operating on an aneurysm because they feared the brain would be too swollen for immediate intervention and might suffer further damage.

Dr. Crowell and his MGH colleagues today believe that getting in and clipping the neck of the aneurysm as quickly as possible is the best way to proceed.

When an aneurysm begins to bleed, there is a 25 to 30 percent chance of a second, more serious hemorrhage occurring. It may come in a few days or in just 15 minutes. The mortality associated with a second hemorrhage is very high.

Experts in neuroanesthesia are now able to shrink a swollen brain very quickly. Advances also have been made in microsurgical techniques and in clips to close off an aneurysm.

"We can even put temporary clips on local blood vessels to release tension on an aneurysm until we can place a permanent clip on it," Dr. Crowell said. "While the blood flow is stopped, we have pharmacologic techniques to protect the brain for up to an hour. Once the permanent clip is in place, we reopen the blood supply."



***Above:*** *Dr. Robert M. Crowell operates to correct an arteriovenous malformation* (A.V.M.).
***Right:*** *In the Laboratory for Cerebrovascular Biophysics, Dr. John Peterson prepares to use a centrifuge separate a blood sample's red cells so that he can study their aging properties for a possible relationship vasospasm.*

Early surgical treatment, which offers good to excellent results to more than 90 percent of MGH patients, not only takes care of the aneurysm, but also facilitates coping with a common complication called a vasospasm. Arteries near an aneurysm often become irritated by its bleeding and constrict, slowing or closing off their own blood flow. MGH research led by Dr. Nicholas T. Zervas, Chief of the Neurosurgical Service, has produced a number of ways to deal with vasospasm *(see sidebar story)*.

Because of an inoperable aneurysm or a coexisting medical problem, surgery may pose an excessive risk to an aneurysm patient. Dr. Crowell then turns to Dr. Pile-Spellman and his colleague, Dr. John K. Chin, to consider the advisability of balloon catheter treatment.

Drs. Pile-Spellman and Chin have already achieved some spectacular successes with balloon treatment for aneurysms. The prospects for wider usage of the method will be substantially increased by the introduction of the G-Ring angiographic system.

A balloon can be employed in one of several ways. If there is good secondary (collateral) circulation, a balloon can be fed into a blood vessel by a tube (catheter) to permanently plug a portion of artery on which an aneurysm has developed. Or, in a more delicate maneuver, a balloon may actually be placed within an aneurysm, relieving the danger of a burst and still permitting blood flow through the affected artery.

When brain arteries become severely narrowed after hemorrhage, expansion of the walls by a balloon (angioplasty) may reverse neurologic deficits.

During 1987 and 1988, Dr. Pile-

Spellman traveled twice to the Soviet Union and spent a total of three months in Kiev studying brain balloon angioplasty under a world expert in this field, Dr. Victor Shchegolov, who has installed balloons in more than 750 aneurysms. Since that training period, Dr. Pile-Spellman has used balloons to treat 25 aneurysms. Some of the patients faced closure of a segment of artery, but in at least eight instances, the vessel was spared through use of the Russian technique or a modification of it.

To determine the advisability of surgery vs. proton beam treatment on an A.V.M. patient, Dr. Crowell and his group confer with Dr. Raymond N. Kjellberg, one of the international pioneers of proton beam, or radiosurgical, care, or with fellow MGH neurosurgeons, Drs. Paul H. Chapman and Guillermo Candia.

An advantage of conventional microsurgery on an A.V.M. is that its successful removal effects an immediate cure. With proton beam, which involves use of Harvard University's 160 million electron volt cyclotron, recovery time may take many months.

On the other hand, the A.V.M. may be very deep-seated. Proton beam radiation eliminates the need for cutting. The therapy also avoids general anesthesia and eliminates any risk of infection.

Proton beam treatment also enables the patient to leave the hospital a day later and avoids the cost of a long hospitalization.

Dr. Crowell said that one of the aims of the new Aneurysm/A.V.M. Center is to study familial aneurysms and see whether it would be possible to break that genetic code.

"We have seen as many as six aneurysms in a single family," Dr. Crowell said.

Dr. Bernd Seizinger, a neurogeneticist at the MGH, examines blood samples from patients known to have a familial aneurysm and looks for a possibly defective family gene. Dr. Seizinger has said that when three siblings in a family are found to have an aneurysm, the chance of breaking the genetic code increases markedly.

Dr. Crowell, who is also Associate Professor of Surgery at Harvard Medical School, said he tends to regard the new center, in a sense, as an institution without walls.

"We really function throughout the hospital," he said. "It requires the collaboration of many people. We have a great group who are not only outstanding in technical skills, but who also know how to function closely as a team." ■

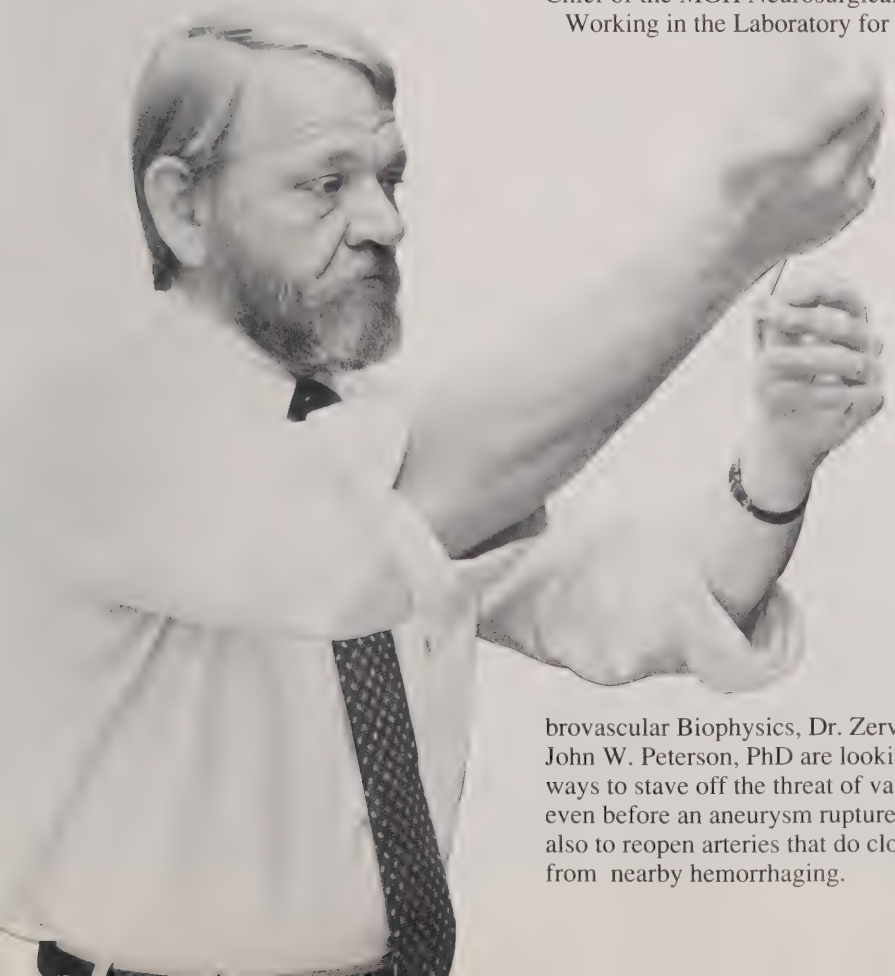
## *Solving the Riddle of Vasospasms*

PATIENTS who survive the rupture of a brain aneurysm often still face a complication that is just as lethal.

Specialists at the MGH and other medical centers have sought for years to learn the mechanism by which bleeding from an aneurysm (or bubble) on the weakened wall of an artery sometimes leads to constriction of other arteries near the site, a process called vasospasm.

"Of those deaths that follow survival from an initial aneurysm, as many can be attributed to vasospasm as to further bleeding," said Dr. Nicholas T. Zervas, Chief of the MGH Neurosurgical Service.

Working in the Laboratory for Cerebrovascular Biophysics, Dr. Zervas and John W. Peterson, PhD are looking for ways to stave off the threat of vasospasm even before an aneurysm ruptures and also to reopen arteries that do close down from nearby hemorrhaging.



In May, the National Institutes of Health awarded the two investigators $2.25 million in grants for the study of vasospasm over the next several years.

"We've felt increasingly that one of the problems of vasospasm involves the body's inflammatory response to a foreign substance," Dr. Zervas said. "In this situation, it would be the presence of blood in the subarachnoid space (beneath a covering of the brain) where it should not be.

"The inflammatory response accelerates the decomposition of blood. We felt that one way to attack the problem was to look for ways of slowing the inflammatory process so that the red cells in the arteries would not be destroyed so quickly. When the cells are intact, they are all right."

Some work already performed indicates that the drug cyclosporine may be an answer. Cyclosporine has been very effective in protecting transplant recipients against rejection of their new organs.

Some years ago, the MGH researchers found that the drug reserpine could alter platelets, the clotting factors in blood, and lessen the likelihood of vasospasm.

The investigators have also examined whether calcium channel blockers, cardiovascular drugs such as Nimodipine, can improve the overall outcome of a ruptured aneurysm by protecting against complications.

Because of its ability to dissolve clots in coronary arteries, TPA (tissue plasminogen activator) is also under study for possible use in disposing of clots that develop around brain aneurysms.

And a laser has entered the research picture. Dr. Kenton Gregory, an MGH cardiologist, has found that the tunable dye laser, pioneered at the MGH for medical uses, can reopen a vasospasm. ■

# *New Guidelines for Early Breast Cancer*

NEW TECHNIQUES that allow doctors to diagnose breast cancer at an earlier, more curable stage have in recent years greatly improved the outlook for patients with the disease.

Five-year survival rates for women with localized breast cancer — tumors that have not spread (metastasis) beyond the breast — now stand at 90 percent, up from 78 percent in 1940 *(MGH News, September 1985).*

But if detection methods and survival rates for early stage breast cancer have steadily improved over the last several years, treatment options have remained, for the most part, virtually unchanged.

For most of the 20th century, the primary method of treatment for localized, early stage breast cancer has been the complete removal of the breast and the lymph nodes under the arm, a procedure called a modified radical mastectomy.

In 1979, this procedure was formally endorsed as the treatment of choice for early stage breast cancer by the National Institutes of Health at its last "consensus development conference" on primary care for breast cancer.

The NIH regularly invites leading specialists to such conferences on various diseases in an attempt to evaluate current research and reach a consensus on treatment.

In June, the Institute held its sixth national consensus development conference on breast cancer. In a startling break from its past recommendation, the conference endorsed breast conservation therapy over radical mastectomies for early stage breast cancer.

"Breast conservation therapy, which we defined as removal of the tumor with about a centimeter of margin and removal of the lymph nodes from under the arm followed by radiation to the breast, is an acceptable method of treating early stage breast cancer and is actually to be preferred to modified radical mastectomy for most women." said Dr. William C. Wood, Chief of Surgical Oncology and Medical Director of the MGH Cancer Center.

Dr. Wood was the chairman of the NIH consensus conference that endorsed breast conservation.

Although some of the larger medical and cancer centers, including the MGH, have increasingly moved away from radical mastectomies in favor of breast conservation for early stage tumors, breast removal has remained the predominant treatment for most women throughout the country.

"You wouldn't think that being here at the MGH," said Dr. Wood, who is also an Associate Professor of Surgery at Harvard Medical School. "We've been doing breast conservation therapy for about 30 years, and increasingly so each year, so that the majority of women are now treated that way here and have been for some time."

Dr. Oliver Cope is the MGH surgeon who pioneered the use of breast conservation. His book, *The Breast: Its Problems — Benign and Malignant — and How to Deal With Them,* published in 1977, summarized Dr. Cope's struggle to convince his colleagues around the world that this procedure was effective as well as preserving of the breast.

"The coastal areas of the country have gone increasingly to breast conservation, but much of the rest of the nation has not," Dr. Wood said.

"The most recent data I've seen shows that about two-thirds of the women with early stage breast cancer have mastectomies, the majority of whom could probably be well-treated with breast conservation."

Cancer specialists define early stage breast cancer as either Stage I or Stage II breast cancer. The disease has four stages in all.

In Stage I, the tumor is no larger than two centimeters (just under an inch), and has not spread beyond the breast.

In Stage II, the tumor is from two to five centimeters (one to two inches), and/or has spread to the lymph nodes under the arm.

In Stage III, the tumor is larger than five centimeters, and involves more of the underarm lymph nodes and/or has spread to other lymph nodes or to other tissues near the breast.

In Stage IV, the cancer has spread to other organs of the body, most often the bones, liver, lungs or the brain.

Although the NIH conference endorsed breast conservation for most women with Stage I or Stage II breast cancer, participants admitted that some of these patients are still best treated with a radical mastectomy.

These groups include women with more than one lump or with deposits of calcium salts (calcification) spread through-

***"The finding that women who receive tamoxifen or chemotherapy have a lower incidence of developing cancer in the other breast over the next few years raises the intriguing question, 'Can we prevent breast cancer, or delay its appearance?'"***

— Dr. William C. Wood

out the breast even microscopically.

Other poor candidates for breast conservation include women with relatively large tumors and relatively small breasts, and women with progressive thickening and hardening of the skin (scleroderma).

The role of radiation and other adjuvant (additional) therapy was also discussed by conference participants. Which patients should receive adjuvant therapy, and how much of that therapy they should receive are two areas of intense research.

"It has been shown over the past 15 years that women who have lymph node involvement benefit in terms of survival by getting adjuvant chemotherapy," said Dr. Wood. "The question is, 'Would that same benefit accrue to women whose lymph nodes are not involved?'"

Dr. Wood said preliminary results from several worldwide trials suggest that node-negative patients who do receive chemotherapy have about a one-third less risk of tumor recurrence than node-negative patients who do not receive the adjuvant therapy.

"But it's still not clear how much their survival will be affected," said Dr. Wood, noting the trials will take several more years to reveal that data.

The NIH Conference made no national recommendation as to whether such node-negative patients should receive adjuvant chemotherapy, instead issuing only broad suggestions on the topic.

*This mammogram of a 52-year-old woman clearly shows a lump 2.3 centimeters (about an inch) in diameter. MGH cancer specialists recommend all women should be screened annually beginning at age 35. The earlier tumors are detected, the better the chances that they can be cured and the breast spared.*

Any decision to undergo adjuvant chemotherapy should include a discussion of the patient's risk of tumor recurrence, as well as the potential advantages and disadvantages of the treatment. Disadvantages include side effects such as nausea, loss of appetite, and thinning or loss of the hair.

One exciting line of investigation currently being pursued in trials is a comparison of chemotherapy with the anti-estrogen drug tamoxifen. Tamoxifen has few, if any, side effects.

Another area of intense study and research is breast cancer prevention.

"The finding that women who receive tamoxifen or chemotherapy have a lower incidence of developing cancer in the other breast over the next few years raises the intriguing question, 'Can we prevent breast cancer, or delay its appearance?'" "If it took chemotherapy to delay its appearance, it would probably not be appropriate. But if tamoxifen can delay the appearance or prevent breast cancer, it would probably be very worthwhile."

Before that question can be answered, the long-term effects of healthy women taking tamoxifen must be determined. That question is already the subject of yet more discussion and future trials.

"Our frustration is that because women with early stage breast cancer do so well, we won't know the results from many of these trials for a decade or more," said Dr. Wood. ■

# *House Calls Can Help Unlock the Panic Prison*

WHEN JOHN S. visited the MGH for the first time last year, he brought his camera to record the event.

"Nobody would believe I was here unless I took pictures to prove it," he told his doctors.

It is not surprising that people who knew John would be skeptical. For 14 years, the 52-year-old former sportscar enthusiast had not once left his home — not even to get the morning newspaper. He was so afraid to leave the house that he would only retrieve the paper if it was delivered close enough for him to reach it with one foot still inside the door.

"I've missed all the good things in life," John told his doctors.

Like a man locked in a jail cell, John was a prisoner in his own house—confined not by iron bars, but by his own fears. For John, there was no hope of parole or time off for good behavior. His was a life sentence because of severe agoraphobia.

Agoraphobia is a Greek word that means literally "fear of the marketplace."

"Over the years, it has come to mean quite a bit more," said Dr. Gary S. Sachs, a staff physician in the Anxiety Clinical Research Program in the Clinical Psychopharmacology Unit at the MGH. "We refer to it here as 'phobic avoidance,' which is really a 'fear of fear itself.' It means avoiding anything out of fear of having a panic attack."

Different situations can cause different levels of anxiety for sufferers *(MGH News,* June 1988). For some, large, busy stores or other open spaces can bring on feelings of panic; for others, airplanes or subways or anything with limited escape routes cause feelings of anxiety. In extreme cases of agoraphobia, the sufferer feels threatened by all places of restricted escape, travel away from home, and being alone.

"In order to assure themselves they won't have a panic attack, they may avoid everything outside the house," said Dr. Sachs.

Little is known about such severe cases of homebound agoraphobia. In some people, the phobia comes on quite gradually; in others, it's a very rapid progression. John had his first panic attack on a shopping trip. First, he simply stopped shopping. But within a very short time, he had stopped leaving the house for any reason.

"Rationally, people know the things they're terrified of are not very frightening," said Dr. Sachs. "But you can't emphasize too much how dreadful these attacks are."

Although MGH psychiatrists and others have been studying panic disorders since the 1950s, relatively little work has been done with the severely homebound agoraphobic. This is not surprising considering how difficult this population is to reach. Since sufferers are unable to

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## — *House Calls*

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leave their homes even if accompanied, they have been automatically excluded from most studies and treatment centers.

Recently, several MGH psychotherapists conducted a study specifically aimed at severely homebound agoraphobics to assess the feasibility of outreach therapy on this population.

The usual treatment for more mild forms of panic disorders has been a combination of anti-anxiety drugs and exposure therapy — inviting the individual to gradually confront the things feared.

"We've had great success treating other forms of agoraphobia," said Dr. Sachs. "But if you can get someone to exposure therapy in a doctor's office they are by definition less ill. But the homebound are so ill, you can't get them to therapy. That's what's made treating them so difficult."

For the MGH study, researchers did interviews for features about the program in local media. Out of about 300 people who responded to the articles, six said they were unable to come to the clinic even if accompanied.

Although the sample size was too small for a significant study, the anecdotal evidence was interesting and has encouraging implications for future outreach efforts.

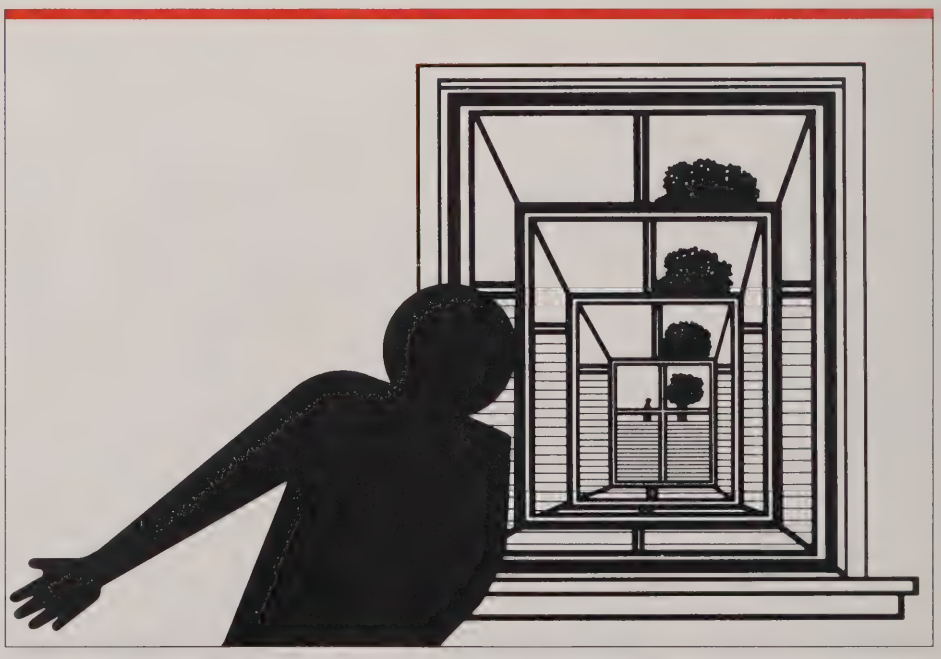
According to the authors of the study, who included Dr. Mark H. Pollack; Dr. Sachs; Dr. George E. Tesar; Dr. Julie Shushtari; Dr. John B. Herman; Dr. Michael W. Otto; and Dr. Jerrold F. Rosenbaum, Chief of the Psychopharmacology Unit, homebound agoraphobics seem to respond to the same treatment once initiated in the home, as do less severely affected people.

Mrs. H. is a 46-year-old married mother of two who had not left her home in four years when she contacted the MGH. When she was unable to come to the clinic for treatment, she was treated at home by an MGH outreach therapist and a physician.

Mrs. H. had her first panic attack, attributed to work difficulties, at age 24. Following that first attack, she continued to experience work-related anxiety and also began having difficulty using public transportation. Eventually, she quit her job. Around this time, she saw a doctor, who prescribed her an anti-anxiety drug (diazepam). Despite the medication, she continued to experience panic attacks when left alone, or when she tried to go out alone. When accompanied, she reported she could go on short trips within the neighborhood. Four years ago, she had a fullblown panic attack while driving her son to school. She has not driven or left her house since. Two years ago, she was treated at home by a psychotherapist for seven months. She felt this was supportive, but she remained unable to leave the house despite the urgings of the therapist.

After Mrs. H. contacted the MGH, an outreach therapist visited her in her home to do an evaluation. The therapist returned several times, spending many hours with her, reassuring her and preparing her for the physician's visit. The doctor prescribed Mrs. H. alprazolam (an anti-anxiety drug). Within several days, Mrs. H. reported feeling less anxious, and began making brief forays from the house in the company of the therapist. Over the next two to three weeks, she spent more time away from the house, and the alprazolam was decreased. Twelve weeks after initiation of treatment, Mrs. H. was able to come to the hospital with a companion.

"It was very gratifying to see how well she reponded," said Dr. Pollack, an author of the study and Director of the MGH Anxiety Clinical Research Unit. "This was a person who had missed out on many of the important events of her life. Some of her neighbors thought she was dead. It was really quite touching to see how treatment could affect such a major change in that woman's life." ■



*Panic attacks strike without warning, bringing intense symptoms of psychological and physical fear in the victim. Symptoms may include sweating; trembling heart palpitations; tingling, choking, or smothering sensations; feeling faint, unsteady, or unreal; and fear of losing control, dying, or going crazy.*

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# Cancer Nursing Rounds: Bringing Theory to the Bedside

THE NURSES and doctors taking care of an MGH cancer patient could not understand why the patient's family was so upset with him.

To his nurses and doctors, the 54-year-old former insurance salesman was a model patient — thoughtful, never complaining, always cheerful and friendly. To his family, however, the man was uncharacteristically irritable. A man who in the past never lost his temper, now blew up at the slightest remark.

Several of the nurses listening to a colleague recount this experience nodded in agreement. They had had similar experiences with patients and their families.

"This was an example of a patient behaving one way when receiving treatment in front of his nurses and doctors and another way at home," Lorrie Powel, RN, an oncology clinical nurse specialist, told the gathering. "The patient the nurse sees may be only one part of the whole picture, just as the patient the doctor sees, or the patient the family sees may be only one part.

"In this case the patient was taking medication that made his mood labile (up and down). Getting more information from the family and the patient led to a change in his medication."

Dr. Donna B. Greenberg, a consultation psychiatrist on cancer patients who participated in this meeting with the nurses, said: "It's important that this information be relayed to the doctor so that the nurse isn't caught in the middle between the family and the patient. The more information everyone has, the wiser the decisions are going to be."

For the next hour Ms. Powel and about 10 other oncology nurses and Dr. Greenberg analyzed the above situation and others like it as they discussed the special informational and psychosocial needs of cancer patients and their families and their roles as nurses in meeting these needs.

The noon-time discussion was part of a weekly series of Cancer Nursing Rounds sponsored by the Nursing Subcommittee of the MGH Cancer Affairs Committee.

Unlike traditional bedside rounds, no patients are involved in these weekly rounds. But patient care, particularly as it relates to the published theory of nursing care, is the driving force behind the sessions.

"What we wanted was a forum where nurses could get together as a group on a regular basis away from the bedside to talk about what's in the literature as it relates to our own experiences," said Ms. Powel, who is also chairperson of the Nursing Subcommittee.

Patricia Ramsey, RN, a graduate student at the Institute of Health Professions (I.H.P.), the master's degree-granting affiliate of the MGH, expanded on the link between nursing practice and nursing theory bridged by the rounds.

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## *New Urology Chief Expanding Department's Horizons*

ALTHOUGH the practice of urology is confined to a small anatomical area of the body (the male and female urinary tract and the male genital organs), it is a specialty on the move.

"Over the last 10 years our horizons have expanded markedly," said Dr. W. Scott McDougal, who will on January 1 become the new Chief of the MGH Urology Service. "The field has become much more complex, much more technical. The tendency now is for people to subspecialize."

Dr. McDougal is well-qualified to manage this growing trend toward subspecialization and more technically oriented patient care without losing the sense of the patient as a person. He comes to the MGH from Vanderbilt University School of Medicine in Nashville, Tennessee where he has been Chief of Urology since 1984. Dr. McDougal trained as a general

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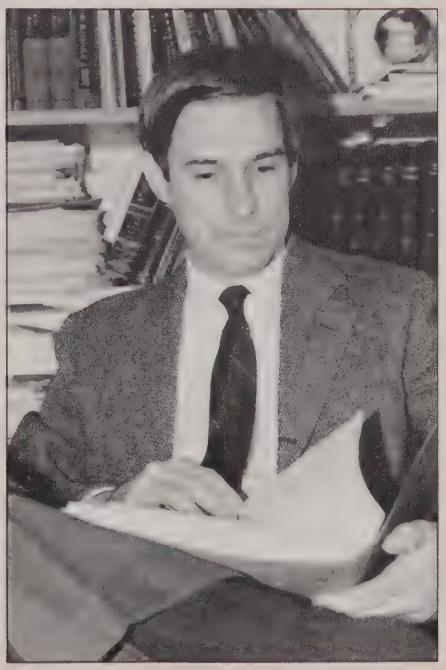

*Dr. W. Scott McDougal*

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EDITORIAL

# The Blot of Infant Mortality

THE HIGH RATE of infant mortality has long been considered a "blot on American medicine." Politicians wanting to restructure the country's health care point out that the infant mortality rate in the United States lags behind that of most of the industrialized world. What seldom is mentioned is that the reason for this high mortality rate is that the American statistics are skewed by the figures for the poor, mostly in inner cities. Absent that, and the mortality rate in the United States is quite respectable. The converse is also true: The ratio in ghettos is a national disgrace.

Just about everyone shares the blame. Perhaps the primary cause is the impoverished nature of our inner cities. If a pregnant woman lives in squalid conditions in subminimal housing; if she is homeless; if she is "doing" drugs or alcohol; if she is unable to afford nutritious food; improved medical care would be relatively meaningless. State governments have traditionally failed to earmark sufficient money so that cities can clean up their ghettos. Cities have not done enough to change the conditions against which the poor struggle. Nor has Washington done enough to help states and/or cities alter the life cycle of people born poor. The federal Women, Infants, and Children program is excellent, but more needs to be done.

Hospitals also cannot claim an outstanding record. It should be no surprise that urban poor seek care in hospitals and neighborhood health centers closest to them. Nor is it a revelation to say that these health care sources are typically operated by grossly underfunded municipal hospitals and that private hospitals, smothered by quixotically bureaucratic, governmental regulations, are wary about venturing beyond their own areas to establish new roots in ghettos. So the poor continue to receive inadequate care and spotty health information. The cause for hope is that medical science and public health care providers have more information than before about nutrition and living conditions as they affect the pregnant. The tragedy is that in days when governments had more money to solve problems governmental priorities were elsewhere. (Often undereducated, the poor tend not to vote.) Now most governments at all levels are themselves struggling fiscally to survive.

Where does that leave women living in ghettos? Certainly the impoverished face even tougher times. Infant mortality is more visible, but the health scene in inner cities is undoubtedly unsatisfactory in many ways. What is needed is a commitment from all levels of government and from the private sector. Business can provide free or at cost some medical materials. Yet many businesses themselves are trying to weather hard times. Health care professionals can volunteer a few hours a week to help the poor. Some are already volunteering in shelters for the homeless and elsewhere, but more volunteers are needed. Yet the physician component of health care workers is already feeling overextended, overregulated, and unloved. Can the besieged governments stop posturing and start creating ways to resolve the problems? What ever happened to VISTA (Volunteers in Service to America)? This country has never more needed a reversion to the spirit of the 1960s. "Ask not what your country can do for you..." Today the first question by Americans is, "What's in it for me?" Is there a spark of the old America left? ■

## — New Urology Chief

*(Continued from Page 1)*

surgeon at Case Western University Hospital in Cleveland and also headed a burn unit at Brooke Army Medical Center in San Antonio, Texas before specializing in urology.

That background helped direct and shape his own particular area of expertise — reconstructive surgery, a subspecialty of urology he wants to more fully develop at the MGH.

"Many of the urinary intestinal diversions we did in the past were done as simple conduits [to channel urine]. Today they are done to improve continence [the ability to retain bodily discharges voluntarily] which can improve remarkably a person's lifestyle," said Dr. McDougal.

New reconstructive surgical techniques, for example, can now often restore normal voiding for a patient whose bladder must be removed for a variety of pathologic conditions.

In the past operations to bypass the bladder were done by simply diverting the drainage of the kidneys to the wall of the abdomen where it was drained into an externally worn bag. Today surgeons can make the patient a whole new bladder.

To accomplish this, surgeons remove the patient's bladder and replace it with a new one fashioned from a piece of the patient's large intestine. Often the patient can spontaneously initiate voiding, however, he occasionally must empty the new bladder himself through a tube (catheter).

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"A true bladder acts to both store and empty urine," said Dr. Barbara Bassil, an MGH urologist. "The bladder we can construct acts as a reservoir."

Other subspecialty areas of urology Dr. McDougal wants to more fully develop and integrate at the MGH include infertility services and neuro-urology, the study of neurology as it relates to bladder function and potency.

Neurologic bladder dysfunction probably most often occurs as a result of spinal cord injuries in which the bladder has been cut off from control of the brain.

But there are many other more subtle examples of situations in which a neurologic disorder can cause a bladder dysfunction (neuropathic bladder), including multiple sclerosis, Parkinson's disease, and tumors involving the spinal cord.

Occasionally the urologist, working in conjunction with other specialists, treats the bladder dysfunction by treating the primary disorder. A Vitamin B12 deficiency, for instance, can cause pernicious anemia, which can affect the central nervous system and lead to loss of control of the bladder. Treat the Vitamin B12 deficiency, and the bladder dysfunction clears up as well.

More often, however, the urologist will treat the neuropathic bladder directly, usually through some form of urinary intestinal surgical diversion.

Other subspecialties of urology that have undergone tremendous changes in recent years include stone management and problems of the prostate.

"There have been many technological advances in recent years," Dr. McDougal said. "These have probably most dramatically affected the way in which we treat kidney stones."

Six years ago most Americans suffering from kidney stones underwent surgery or some other invasive procedure to remove the stones. Patients usually had to spend a week in the hospital and another three to four weeks convalescing at home.

In 1984, the MGH became one of six hospitals in the country to begin breaking up kidney stones nonsurgically. Using a device called a lithotripter, surgeons crushed the stones through externally transmitted shock waves *(MGH News, October 1988)*. Patients could be treated the same day and return to work after only two or three days rest at home.

"There's no comparison with surgery," said Dr. Niall M. Heney, an MGH urologist. "It's a horse of a different color."

Today lithotripters are so widely available in hospitals around the country, they have made open surgical removal of kidney stones almost unknown.

But while kidney stone management has moved away from open surgery, Dr. McDougal said other subspecialties such as prostate surgery have moved in the other direction.

Ten years ago urologists primarily used radiation therapy to treat problems of the prostate — a male organ that encircles the canal (urethra) that carries urine from the bladder through the penis and out of the body.

But one of the major side effects of radiation therapy was impotence. This consequence led many men to avoid any treatment at all rather than risk losing their potency.

"Over the past decade the development of new surgical techniques has allowed us to remove the prostate and at the same time assure continency and potency," Dr. McDougal said.

The new techniques have led many men who would have avoided treatment in the past to seek medical attention. Today prostate surgery accounts for about half of a urologist's practice.

Improving the Urology Service's already outstanding patient care — a national poll of physicians by *U. S. News & World Report* earlier this year rated the MGH one of the 10 best hospitals in the country for urology — is only one of Dr. McDougal's goals. He is also committed to research and to teaching.

Dr. McDougal's personal research interest is in understanding transporters — how various electrically charged atoms (ions) are transported across thin layers of tissue (membranes).

In reconstructive surgery urologists frequently use portions of the intestines as a conduit or storage vehicle for urine. Ideally, however, a tissue that is used to store urine should not transport substances. But the primary function of the intestines is reabsorption.

"The intestines weren't meant to serve in a storage function," Dr. McDougal said. "My interest is to understand how some of these substances are reabsorbed by the intestines and how we can prevent that from causing any untoward metabolic derangements."

Dr. McDougal, who will in addition be a Professor of Surgery at Harvard Medical School, also wants to establish a major residency training program in urology at the MGH "I'm very committed to teaching. I think this has the potential to be one of the finest residencies in the country.

"But everything hinges on patient care," Dr. McDougal continued. "If you have excellent patient care, a large patient population, and excellent patient services, then the rest of it all falls into place." ■

*New Chief of Urology Dr. McDougal at work in his office.*

# Kidney Transplants at the MGH: 1,000 and Still Counting

***Top:*** *Kidney transplant recipient Jerome Szydlowski (left) is shown with his brother and donor Leonard at Mr. Szydlowski's home in Milwaukee a few months after his operation in April 1963.*

***Bottom:*** *Dr. Francis Delmonico transports a recently donated kidney to the operating room.*

WHEN Jerome Szydlowski, 34, of Milwaukee, checked into the MGH in April 1963, his doctors gave him only a short time to live. "He was failing very rapidly," said Dr. Paul S. Russell, the former Chief of the Transplantation Unit at the MGH. "He had all the effects of terminal uremia. He was very weak, and his vision was so bad he could not even read the headlines in the newspaper."

Until that time there was little doctors could do for patients with acute kidney failure like Mr. Szydlowski.

Dialysis, if it was available at all — and it was not then at the MGH — was a primitive and very expensive technology.

And even if dialysis had been available, it was a major technical challenge to maintain access to the blood to permit repeated dialysis over a long period of time.

Until about that time a patient's blood had circulated into the dialysis machine through a catheter temporarily inserted into a major blood vessel. Following the treatment, surgeons removed the catheter and reconstructed the blood vessel, a process that could not be repeated very many times.

Only when little teflon tip "shunts" were developed that permitted a permanent short circuit between an artery and a vein outside an arm or a leg, which could then be attached repeatedly to tubing leading to a dialysis machine, was somewhat longer life support possible.

A year after Mr. Szydlowski's admission to the MGH, Dr. George P. Baker, Jr. helped establish the hospital's Hemodialysis Unit and served as its first director from 1964 to 1974. Dr. Nina E. Tolkoff-Rubin is the current Director of the Hemodialysis and the Continuous Ambulatory Peritoneal Dialysis Units and also Medical Director of the Renal Transplant Program.

The MGH organ transplant effort began a few months after Dr. Joseph Murray's team at the Peter Bent Brigham Hospital had shown that the drug Imuran, discovered at the Burroughs-Wellcome Company, was effective in controlling the immune rejection reaction to transplanted kidneys.

And so on April 23, 1963, a team led by Dr. Russell transplanted a kidney donated by Mr. Szydlowski's brother Leonard into Jerry. Mr. Szydlowski received Imuran and a cortisone derivative to maintain his transplanted kidney.

Within a few days the donor kidney began to function, and Mr. Szydlowski quickly began to improve.

"Jerry just started to bloom," Dr. Russell said. "He was like a different person. He started to read the newspaper, to laugh a lot. The change was remarkable."

After the operation Mr. Szydlowski moved back to Milwaukee where he lived 11 years. He died of an unrelated cardiac condition.

Jerome Szydlowski was not the first kidney transplant recipient at the MGH (three patients preceded him), but his remarkable success ushered in a new era for kidney transplantation and for organ transplants in general, at the MGH.

Twenty-seven years after the effort began, MGH surgeons carried out the 1,000th kidney transplant at the hospital.

Robert Neveu, a 44-year-old father of two from Merrimack, NH, received his new kidney and opportunity for a new life on August 20, 1990. Unlike Mr. Szydlowski who faced an uncertain future, Mr. Neveu has a better than 85 percent chance of success with his new organ.

"There's been improvement year by year and decade by decade," said Dr. Francis Delmonico, Director of Renal Transplantation at the MGH, who recently completed a two-year study of all 1,000 kidney transplants at the hospital. "The progress we've made has really been quite extraordinary."

Even more significantly, the organ transplant program that began by nursing patients in a double room that was previously a special operating room on White 12, now occupies the entire top floor of the Phillips House and involves specialists from several different disci-

plines. Surgeons associated with the Unit now carry out every kind of "solid" organ transplant procedure, including heart, liver, kidney, pancreas, bone, and most recently, lungs. Bone transplants are carried out on patients staying on orthopaedic floors.

Kidney transplants came first, not only because the operation is technically the most straightforward of all transplant procedures but also because surgeons were able to use living related donors, thus making organs in excellent condition available while also easing the risk of rejection in the era before drugs powerful enough to suppress the immune system reliably were available.

*A kidney transplant procedure*

The earliest successful kidney transplants had been carried out between identical twins. Since they are genetically identical, rejection by the immune system was avoided completely. Close living relatives were the next best candidates.

"We knew in general from animal experiments that genetic closeness was a good thing, but we had no way of selecting donors from a certain genetic category because we had no tissue typing of any kind," said Dr. Russell, who is also John Homans Professor of Surgery at Harvard Medical School. "We couldn't tell if a sibling or a parent was more compatible as we now can with great precision."

The lack of preservation techniques for organs also made using living donors preferable for the early transplants.

"Today the kidney can be preserved up to 60 hours after it's removed from a donor," Dr. Delmonico said.."We couldn't do that 25 years ago."

By the late '60s improving donor selection methods (mainly through tissue typing — a procedure in which a potential donor's white blood cells are matched against those of a recipient to test for compatibility), combined with the growing acceptance of the diagnosis "brain dead," led to the use of cadaver donors.

Today nonliving, unrelated donor kidneys make up the majority of the kidney transplants done at the MGH and around the world.

Other advances have come in the development of anti-rejection drugs.

Before 1963 the only treatments doctors had at their disposal to ward off rejection of the donor organ were steroids and whole body radiation. After the introduction in 1962 of Imuran, the first chemical immunosuppressant, a number of increasingly effective agents have been developed. The MGH team has been especially active in the discovery and testing of antibodies to lymphocytes, the principal cells causing rejection. The first of these was anti-thymocyte globulin (ATG), which was made in horses against human cells. This is a valuable agent and is still sometimes used.

In October 1980 the MGH became the first institution in the world to study and use OKT-3, which is a powerful agent, a monoclonal antibody directed specifically against the cells which cause rejection. Six years later, this material was approved for regular patient use. It is widely used around the world in transplant patients to treat severe rejection once that process has already started.

"We don't normally use it for the treatment of chronic rejection," said Dr. A. Benedict Cosimi, who led the team that first used OKT-3 at the MGH and who later succeeded Dr. Russell as Chief of the Transplant Unit on January 1, 1990. "What it seems to be best at is reversing active rejection."

Once the rejection is reversed with OKT-3, it usually does not recur.

Another major drug developed to treat rejection is cyclosporine. Unlike OKT-3, cyclosporine is used to prevent rejection. Transplant patients now remain on the drug the rest of their lives.

Since the introduction of these drugs, one-year survival rates for kidney transplants have risen dramatically. The MGH now has an overall one-year survival rate for kidneys obtained from cadaver donors of 86 percent, and over 90 percent for those from related donors. At the same time survival rates have shot up, the cost of the operation has steadily come down.

Today the cost of a kidney transplant is about $30,000, said Dr. Delmonico. Even with the $4,000 to $5,000 annual cost of cyclosporine, the operation is still significantly cheaper than dialysis, which runs about $23,000 a year according to 1988 figures, the most recent available.

"But cost isn't the only consideration," said Dr. Delmonico, who is also an Associate Professor of Surgery at Harvard Medical School. "The kidney function provides so much in terms of a person's total well-being, not to mention the freedom of activity a person has compared to remaining on dialysis three times each week. In terms of a patient's quality of life, there's no substitute for a kidney transplant."

Dr. Delmonico said the major future advances in kidney transplantation will continue to be made in new and better immunosuppressants and a better understanding of the rejection process.

Much research is also being done in the area of cross-species (xenogeneic) transplantation. Dr. Hugh Auchincloss of the MGH is a leader in that research.

"Cross species transplantation could conceivably be applicable for certain kinds of purposes relatively soon," Dr. Russell said. "Specific tissues like the islets of Langerhans of the pancreas, which make insulin, would be physiologically pretty much the same from one species to another.

"We're also doing a lot of very precise, detailed research on the biology of transplant rejection. For instance, we're trying to teach cells by genetic manipulation to make things that the body itself doesn't make.

"It's all part of transplantation of the future. Over the years, it's a field that's developed immensely." ■

# — Cancer Nurses Bringing Theory to the Bedside

*(Continued from Page 1)*

"All of our direct care is based on research findings," Ms. Ramsey said. "We don't do something a certain way simply because it's always been done that way. We do things a certain way because it's been proven that that's the best way to do it.

"These Cancer Nursing Rounds are one way for us to share new knowledge about our profession and new ways of doing things that we can take back and apply practically in our patient care."

*Mimi Bartholomay, RN, an oncology nurse specialist, prepares to give Dora Watkins an antibiotic intravenously. Mrs. Watkins, formerly of Danville, VA, who now resides in Dorchester, MA, is a leukemia patient in the MGH's new Ellison Building.*

Camille Madden, RN, and Deborah Mayer, RN, members of the Cancer Nursing Affairs Committee, came up with the idea for the rounds last year. Although other nursing forums have been held at the MGH, they were usually more informal and held only occasionally. These are the first regular weekly rounds at the hospital directed at nurses and their particular concerns.

"Getting together every week to talk about our profession is just not something nurses are used to doing," Ms. Powel said. "But we wanted to impress on people right from the beginning that these rounds are part of their practice; to incorporate them into their schedules. It's the only way we felt we could accomplish our objectives."

Although the weekly rounds are open to all nurses at the hospital, they are specifically targeted at oncology nurses and the particular demands the nurses face in caring for cancer patients.

The sessions are structured around the 11 "outcome standards" drawn up by the Oncology Nurses Society and the American Nurses Association. These standards represent 11 high-incidence problem areas common to caring for cancer patients. They include: prevention and early detection, information, coping, comfort, nutrition, protective mechanisms, mobility, elimination, sexuality, ventilation, and consolation.

While these are problems common to every patient, they are often more pronounced for those with cancer.

"A lot of times the cancer patient has more emotional problems than other patients," said Julie Allen, RN, who cares for a variety of patients, including cancer patients, on the fourth floor of the hospital's Phillips House Building. "Cancer patients often have more coping and more emotional needs."

Knowledge gaps about the disease process and the risks and benefits of treatment are also sometimes more pronounced with cancer patients. The level and amount of family involvement can also be different and sometimes more intense because of the coping and emotional stresses of the disease.

"For a lot of patients and their families, 'cancer' is a very scary word," Ms. Allen said. "Family involvement sometimes is very stressful."

For each of the 11 standards, there is a desired outcome for the patient. Under "information," for instance, the outcome standard is that "the patient and the family possess knowledge about the disease and treatment in order to attain self-management, participation in therapy, optimal living, and if the disease is incurable, peaceful death."

A woman about to receive chemotherapy who does not understand the risks and benefits of the treatment is an example of a patient with an information deficit related to her treatment.

A parent with cancer who does not know how to talk to his or her child about the disease is an example of a patient with a more personal kind of information need.

A patient from a different country and a different culture represents yet another kind of information need and challenge.

Under "Coping," the desired outcome standard is that "the patient and family, while living with cancer, manage stress within their individual, physical, and psychological capacities and their value systems."

Stresses come in all different shapes and sizes for the patient and the family living with cancer.

A woman who loses a breast to breast cancer is an example of a patient whose stress may come from an altered self and body image.

A father wth cancer may experience a different kind of stress brought on by worry about providing for his family.

"In every nursing situation, the health-care providers, including the doctors, the nurses, the therapists, the patient and the family, form a team," Ms. Powel said. "We're all trying to help the patient deal with a particular problem as it impacts on his or her life. The nursing rounds are a way for us to share our practical experiences, as well as explore pertinent research, in order to better help the patient to get the best possible care."

A different outcome standard is discussed each month. In September the topic was "Prevention and Detection." For this standard, presentations tended to be more formal. One was a lecture on "The Role of Mammography in Early Detection of Breast Cancer." Another was a lecture on "Cancer Epidemiology, Prevention, and Detection."

Other standards lead to more informal discussions. In November, for instance, the topic was "Coping." Presentations ranged from a discussion of the psychosocial needs of the relatives of cancer patients to a discussion of the particular coping needs of AIDS patients. "Oncology nurses are taking care of a lot of AIDS patients these days," Ms. Powel said. "It's a natural position for them

because so many of the issues, such as coping, are germane to both populations."

On the last Wednesday of each month, a case study published in one of the nursing journals and relating to that month's topic is discussed in detail.

Attendance at the rounds averages about 10 to 12 nurses, although standing room only crowds of 40 or more are not unusual. Attending nurses receive continuing education credit that can be applied toward their annual license renewals.

"Nurses spend most of their time at the bedside," Ms. Ramsey said. "Yet their practice is based on information. This forum provides an opportunity to present the most current information. The idea is that the nurses can then take that information back to the bedside and apply it on a practical basis." ■

# *Acne: More Than Just Skin Deep*

ACNE, one of the most common skin problems in the United States, is also still one of the most misunderstood.

The American Academy of Dermatology states that 85 percent of all Americans between the ages of 12 and 25 are afflicted with the embarrassing blemishes that characterize the disease.

*"You cannot emphasize too much the emotional toll that this disease can have on young people."*

*— Dr. Lynn Drake*

Yet despite the large numbers of sufferers, myths and misperceptions about acne abound. Topping the list of myths is that certain foods cause acne. For many years, foods such as chocolate, french fries, peanuts, and cheese were blamed for acne.

Skin specialists (dermatologists) now know this is not true. Diet is not linked to acne. Instead, the causes of acne are more complex and usually involve multiple factors.

Another common misperception about acne is that only teenagers suffer the embarrassing blemishes. Although the peak prevalence is at age 17, acne may begin as early as age 8, and is not uncommon in the 10- to 12-year-old group. Adults, too, and especially adult women, suffer acne eruptions.

But probably the biggest myth of all about the disease is that acne is only skin deep.

"You cannot emphasize too much the emotional toll that this disease can have on young people," said Dr. Lynn Drake, Deputy Chairperson of the Department of Dermatology at the MGH. "It can be a devastating disease. There have even been suicides reported. That's what's so frightening about it. People think it's just a little acne, but it's not just a 'little acne.' It can really interfere with a person's lifestyle and social development."

Acne occurs mainly on the face, chest and back. These areas of the body are most susceptible because they have large numbers of oil glands known as sebaceous glands. At puberty, when the human body is maturing from child to adult, hormonal changes cause sebaceous glands to get bigger and produce increased amounts of an oily substance called sebum. Bacteria on the skin acts on sebum to produce irritating substances which speed up the growth of cells in the pores. Dead skin cells, sebum, and bacteria clump together to form a plug called a blackhead (comedone). Blackheads, which result from exposure of the oils to air, not dirt, tend to lead toward the formation of pimples, which can be either little red bumps (papules), or little white bumps (pustules), or both.

*A young man "before and after" systemic drug treatment for acne.*

The largest percentage of patients with acne suffer mild to moderate eruptions of blackheads and pimples. Young men and young women are equally affected. Most cases of acne subside completely within a few years of their onset. A few cases remain active into adulthood.

For a small percentage of patients, however, the acne is so severe it can scar them physically and emotionally for life.

Severe (cystic) acne is marked by large, inflamed cysts or sores that often bleed and can become infected. Both men and women are affected, although males have, on average, greater degrees of severity.

While much still needs to be learned about acne, in recent years, researchers have uncovered considerable new knowledge about what causes the disease and how to treat it. Some of that research is taking place at the MGH.

This year alone, four patient studies have been, or are about to be, conducted at the MGH on acne. "We now know that acne is not a single factor disease," said Dr. Drake, who is also Director of the Clinical Investigations Unit for the Department of Dermatology. "There are usually several things going on at the same time that cause acne."

In the case of adult women, for instance, the acne may be a signal for a more serious underlying hormonal imbalance. Treat the underlying problem and the acne clears up as well.

In other patients, the causes can be numerous — a combination of genes, hormones, and cosmetics, with a little stress thrown in for good measure.

"We've gotten much better at pinpointing all the multiple factors," said Dr. Drake. "We're much more likely to think in terms of how the whole body is relating to an individual's disease, in this case acne."

At the same time diagnosis of the causes of acne has improved, so have treatment options and results.

The discovery of retinoids (the class of drugs derived either naturally or synthetically from Vitamin A), and in particular, the systemic (oral) retinoid, isotretinoin, have revolutionized the care of acne patients.

Until isotretinoin (which is marketed under the brand name Accutane) was approved for dermatologic use in 1982, doctors treated severe cystic acne with almost anything they thought would help,

*(Concluded on Page 8)*

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## —*Acne*

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ranging from topical preparations to systemic antibiotics, some of which had very severe side effects. Success was largely hit or miss and well under 50 percent.

In the mid-60s, the first topical retinoid — tretinoin or retinoic acid — was approved for the treatment of acne. Retinoic acid works by helping to keep the cell turnover active. As the skin matures, the dead cells migrate to the outer layer of the skin and accumulate. Retinoic acid helps strip off these dead cells and keep them from piling up on the surface. Although many patients complain about dryness and skin irritation, retinoic acid has proved very effective in treating mild to moderate forms of acne eruptions.

"The real importance of retinoic acid was that it introduced us to the notion of treating acne with retinoids," said Dr. Drake. "That's one of the areas where the future of acne treatment lies. Additionally, there are several other new classes of drugs that are being investigated and hold some promise for new therapies."

Retinoids are defined by their chemical configuration. In their synthetic form, there are at least 2,000 different derivatives. In addition to treating acne and other skin diseases, retinoids are also being investigated as possible cancer preventives.

"They are one of the most exciting classes of new drugs we have right now," said Dr. Gary L. Peck, the investigator who while at the National Cancer Institute did the original work in the late 1970s on Accutane.

The only other retinoid approved for the treatment of acne, Accutane works by inhibiting the secretion of sebum.

"Accutane changed the lives of many young men and women," said Dr. Drake. "It cures acne."

For the majority of patients, a single, 20-week treatment is all that is needed with Accutane. Occasionally, a patient will suffer a minor recurrence of the disease and require a second, 20-week treatment.

"It is the most potent drug we have right now for acne," said Dr. Peck, who resides in Maryland.

It is also the most toxic. The drug can cause severe adverse side effects, including very dry and peeling skin, nose bleeds, chapped lips, high levels of fats in blood, and most seriously, birth defects when taken by pregnant women. Because of these side effects, a major goal of much current acne research is finding a less toxic, but as effective, substitute for Accutane. Much of that investigation is focusing on topical retinoids. Of the four acne studies at the MGH this year, three have involved new topical retinoid drugs.

"It would be wonderful if we could develop a topical drug to treat cystic acne," said Dr. Drake. "That's everybody's goal."

Still other investigators are looking at retinoid derivatives as possible topical treatments.

"There is no limit to the chemical variety of retinoids that you can make in the laboratory," said Dr. Peck. "But it takes time to test all of them. We'll be looking at this class of drugs for years."

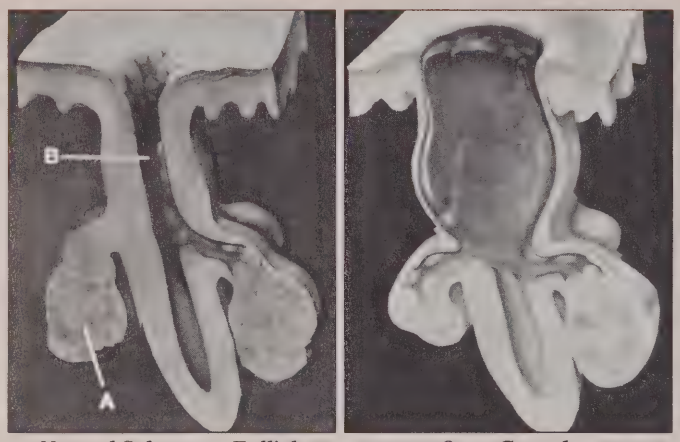
In addition to treating the disease process, advances have also been made in treating the physical scars that remain after the acne subsides.

Many acne scars can now be removed with chemical peels that remove the outer layer of skin, or through a process called dermabrasion. In this procedure, the specialist uses a tiny grinding wheel to literally sand off the outer layer of skin.

For deep "ice pick" scars, surgery is often the only recourse. Using a tiny instrument with a sharp, circular tip on the end, dermatologists remove the scar and replace it with a little graft taken from behind the patient's ear. After the area heals, it can then be dermabrased smooth.

"Frequently we can give a patient a very nice cosmetic appearance using some of these newer surgical techniques," Dr. Drake said. ■

## *How Pimples Are Formed*




***Normal Sebaceous Follicle*** ***Open Comedo***

*PIMPLES ARE FORMED when hormonal changes cause sebaceous glands (A) to get bigger and produce increased amounts of an oily substance called sebum. Bacteria on the skin acts on sebum to produce irritating substances which speed up the growth of cells in the follicular canal (B). Dead skin cells, sebum, and bacteria then clump together to form a plug called a blackhead (comedo). Blackheads, which result from exposure of the oils to air, not dirt, tend to lead toward the formation of pimples.*

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# Research Grant Spurs Work on Nerve Cell Regeneration

FOR YEARS scientists have struggled to understand why the nerve cells of newborn animals grow and repair themselves so much better than adult nerve cells.

The likelihood, say scientists studying the question, is that the newborn has parts of the developing program still "turned on" inside its cells. The challenge then becomes how to unlock the secrets of that program: why it turns itself off in the adult and how to turn it back on again.

At the same time this investigation has been going on inside the cell, other scientists are struggling to understand the role of external stimuli on nerve cell growth. Why, for instance, does a central nerve such as the optic nerve not grow if it is damaged? But why will that same damaged optic nerve begin to grow again if it is attached to a noncentral (peripheral) nerve with a different set of stimuli outside the cell?

"For years we've had a dilemma in the field of developmental biology [the study of how a single cell or egg becomes a whole animal]," said Dr. Mark C. Fishman, Chief of the MGH Medical Services Developmental Biology Laboratory. "On the one hand we have a school of people talking about intrinsic [inside the cell] programs of growth. On the other hand we have hundreds of labs looking at all the different kinds of external stimuli you can put on cells and make them grow.

"But we've had no way of integrating the two. We've had no way of coordinating these intracellular programs and the

*(Continued on Page 4)*

*Dr. Mark C. Fishman, Chief of the MGH Medical Services Developmental Biology Laboratory, recently received a $4 million research grant from two Japanese companies to support Dr. Fishman's research on nerve cell growth and regeneration.*

## *Medicine on Trial: Law & Psychiatry Meet in New MGH Service*

ON THE SURFACE, law and psychiatry would seem to have little in common. One is often practiced in a courtroom, and the other in a general hospital or psychiatric institution. A law degree is needed to practice the former; a medical degree, the latter.

But increasingly, these two disparate fields have begun to overlap. And the setting for that overlap can be as commonplace as the home, the workplace, the schoolyard, a public street, or a tavern.

"Mental illness is something that cuts across all of society. It can affect anyone," said Dr. Ronald Schouten, who holds a law degree as well as a medical degree. "And anyone, it seems, can get involved in the legal system at one time or another whether it's a divorce, a child custody case, a personal injury suit, or a major crime."

A new Law & Psychiatry Service headed by Dr. Schouten hopes to make the transition between the two professions easier. The new service, which is part of the MGH Department of Psychiatry, has as a major goal the training of mental health professionals to provide expert consultation to the courts whenever medical issues bump up against the law.

The centerpiece of the new LPS is its forensic psychiatry services. Forensic psychiatry is defined as the direct interaction between psychiatrists and the legal system. For many people, forensic psychiatry conjures up images of the old television medical detective Quincy solving complicated, sensational crimes that baffled the local police force.

"I think that image was typical of

*(Continued on Page 2)*

## INSIDE

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EDITORIAL

# The Psychiatrist and the World of the Court

In this world of specialists, what chance does the generalist have? Increasingly little. In medicine the talented generalist can diagnose and treat the relatively common disease. He can usually diagnose the less common ailment as well and knows when to steer a patient to the right specialist for definitive diagnosis and treatment. Even the specialist these days often points the patient to a subspecialist. A cardiologist, for example, will frequently refer a patient with an irregular heartbeat to a cardiologist subspecializing in arrhythmias.

Physicians of all types and specialties are almost all generalists when it comes to the law. After all, medicine is an art, not an exact science. But the law often demands a definitive answer, something which even the most precise science cannot always provide. It is thus virtually impossible for a physician to satisfy judge, jury, prosecutor, or defense lawyer. Perhaps the most vulnerable of all is the psychiatrist. Physicians in most other areas can confirm their diagnoses with Xrays, scans, and laboratory tests. Psychiatry has no good diagnostic tests. While psychiatry is discovering much that is new, it has to contend with that most extraordinary of organs, the human brain. The psychiatrist deals with the dark recesses of the mind. Not even the marvelous new scanning devices can penetrate the mind, uncover motives, or precisely relate a specific anatomical finding to a psychiatric disorder—at least not yet. Regardless of specialty, predicting when a very sick patient is going to die—or even if the illness is fatal—is at best chancy. But compared to the tools of psychiatry, some physicians are today armed with tools with the precision of a nuclear clock.

Now put the psychiatrist or any physician in a courtroom and subject that person to the harassment of a wily legal adversary. Add the desire of the legal system for black and white answers, not gray; and you have a specialist at the mercy of a legal specialist, to wit, a lawyer.

It was partly with this scenario in mind that the MGH developed its new Law & Psychiatry Service. The founder is both a physician and a lawyer. With these dual degrees Dr. Ronald Schouten is able to view the courtroom from both vantage points. By teaching the psychiatrist how the world of the law—especially the courtroom—operates, Dr. Schouten can strip the trial of its Masonic-like mysteries. He can also teach what kinds of information are relevant to the courtroom. So armed, the psychiatrist–legal expert should become a better, more helpful, and more relaxed witness. ■

## —*Law & Psychiatry*

*(Continued from Page 1)*

forensic psychiatry in the past," said Dr. Schouten. "But in recent years it has come to mean much more than just criminal cases. Today, it includes everything from family matters to personal injury cases to issues involving risk management, administrative work, confidentiality, competency to stand trial, ethical issues, moral issues, as well as criminal cases."

Just a partial listing of recent LPS cases bears out Dr. Schouten's assessment. In many respects, it reads like the front page of the daily newspaper:

A death penalty case, a personal injury suit, a child abuse case, a worker's compensation suit, a dangerous worker case, a competency to stand trial case, a bail hearing case, a contested will case, a civil commitment case.

In each case, an attorney or a judge has asked a participating LPS psychiatrist for a medical opinion regarding the mental health status of an individual involved in the case.

Although the legal system has a specific question it wants the medical professional to answer — such as whether or not a person is competent to stand trial — many consultants attempt to answer the question without knowledge of the legal issues, the elements of the question, or the need for a structured approach. Dr. Schouten pointed out that this can lead to problems.

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PHOTOGRAPHS: Page 1, Courtesy of Dr. Fishman; Pages 3, 8, Linda Goodspeed; Pages 4, 5, Denise Marshall, Orthopaedic Media Department, MGH; Neurons, Page 5, Courtesy of Dr. Strittmatter; Page 6, Kennetha Bigham.

"One of the problems we have with forensic psychiatry," Dr. Schouten said, "is that often people will be contacted and decide they will accept the job as expert witness with no background in the field."

The result, said Dr. Schouten, can be an evaluation that ranges anywhere from 1 page to 20 pages. Either extreme may be equally useless.

"The goal of the LPS is to set up a specific training program for doing these kinds of evaluations and consultations," Dr. Schouten said. "All of our people are highly trained medical professionals. We provide them with the legal framework to use that medical training.

"It's really an attempt to provide quality control; a more standardized product, if you will. There's still a lot of room for individual creativity, but in every evaluation there's a need for the mental health professional to be very focused in order to be able to provide clear and useful information to people."

In addition to providing training in forensic consultation work, the LPS can also draw on a core group of highly experienced expert witnesses for more complicated cases. "We're working on a death penalty case right now," said Dr. Schouten. "I would not want to give that kind of situation to anyone not a very experienced clinician. We have that kind of experience we can draw on."

Some people argue that psychiatrists and psychologists do not belong in the courtroom at all. According to these critics, mental health professionals do not make good witnesses because the legal system demands they answer questions with a greater degree of certainty than their science allows or provides.

The Hinckley trial 10 years ago, more than any other single event, probably helped shape public opinion against the use of psychiatrists in the courtroom. The acquittal of would-be presidential assassin John W. Hinckley Jr. on grounds of insanity led to widespread public outrage, a change in the insanity defense, and worst of all, from the mental health profession's point of view, a loss of credibility.

"People were saying, 'Look at those psychiatrists contradicting each other,'" Dr. Schouten said. "But I think it's an unfair criticism, and one you can make of any other profession. Put two economists in a courtroom and the joke is you'll get three opinions. The same is true of engineers or other professionals.

"What you are really criticizing is the legal system in general and the whole adversarial process. It's not a perfect system, but so far, it's the best we've got. And objective, qualified mental health professionals can help it work better. While theoretically it would be nice if our services weren't needed, the truth is there is an increasing need by judges and attorneys to help them sort out this information."

*While there are other such "forensic psychiatry" services in the country, Dr. Schouten said the new LPS is the only one he knows of with access to such a wide range of clinical specialists.*

*"Other programs offer what you might call 'forensic generalists' — one person who does all the forensic work," Dr. Schouten said. "We can offer access to specialists in a variety of clinical fields."*

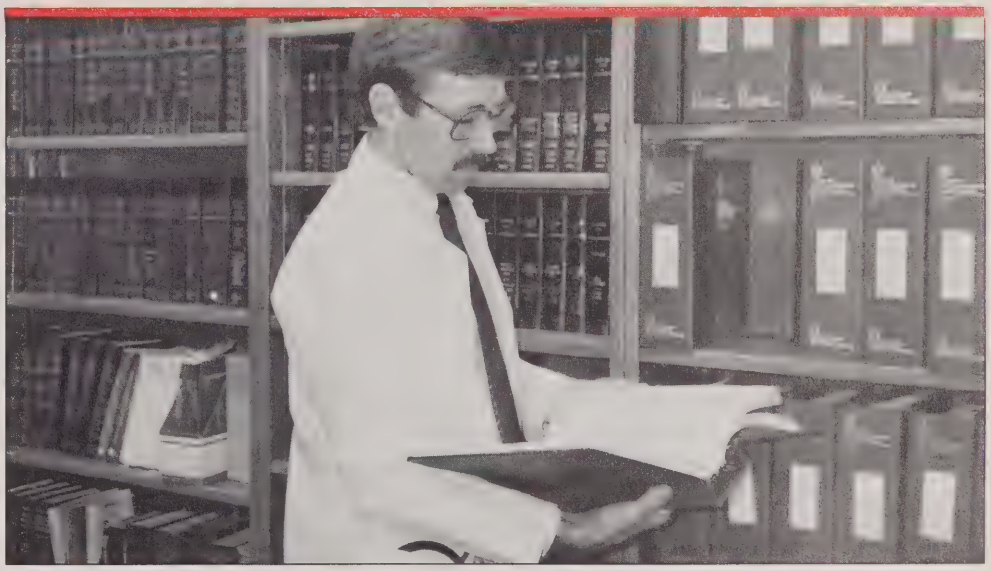
Out of a core group of about eight psychiatrists and psychologists, Dr. Schouten can draw on experts in child psychiatry, for instance, or antisocial behavior, psychopharmacology, or neuropsychiatry.

More recently the LPS initiated a second seminar series targeted specifically at members of the mental health profession. Topics range from legal to ethical to medical issues. A sampling: "Mental Health Professionals and the Law"; "Ethical Considerations in Forensic Psychiatry"; "Violence Toward Therapists."

"The goal is to provide a level of teaching about the legal system for our department and for other departments, so that when people bump into the legal system as they invariably will, there will be a higher level of comfort and a lower level of anxiety," Dr. Schouten said.

The research component of the new LPS is just beginning to be formulated. Currently the service is involved in two comparative studies of "the interactions between the law and modern medicine."

One of these is a study of the criminalization of HIV (AIDS) transmission; the other involves legal approaches to informed consent. Both projects are being conducted in conjunction with Professor Stefano Canestrari of the University of Bologna.



*Dr. Ronald Schouten, the Director of the new Law & Psychiatry Service, researches a legal case at the MGH law library.*

Beyond simply providing forensic training and consultation to the courts, the new LPS also has teaching and research objectives.

The consultation work is built around staff teaching and training. But other educational opportunities seek to cast a wider net and involve more in-house personnel and departments beyond the Department of Psychiatry.

One of these efforts is a weekly seminar series. The talks are given by legal professionals and forensic mental health specialists and are open to all hospital staff. Some sample topics: "Competency, Informed Consent and the Right to Refuse Treatment," "The Insanity Defense and How It Grew," "The Civil Commitment Process."

"There's a lot of potential for more research in forensic psychiatry here. We're just laying the groundwork for that now," Dr. Schouten said.

To date Dr. Schouten said the response by the medical and legal community to the new LPS has been very positive.

"We were right. There is a real need for this kind of service out there. Judges and attorneys want to turn to someone they can trust. They don't want to go through a telephone book when they need a psychiatrist. They want a known quantity. And that's what we can provide them." ■

# — Research Grant Spurs Work on Nerve Cell Regeneration

*(Continued from Page 1)*
external environment."

Until recently. Intriguing discoveries in Dr. Fishman's laboratory over the last several months are bringing investigators closer than ever before to reconciling this age-old dilemma and unlocking the secrets of nerve cell growth and regeneration.

How nerve cells grow and repair themselves has baffled scientists for hundreds of years. The inadequacies of the adult nervous system to repair itself is a problem that permeates medicine. The absence of nerve growth in the injured adult central nervous system is the critical block to recovery from stroke or injury. Even in the noncentral (peripheral) nerves, where some nerve cell growth does occur, repair is often

*Dr. Dario Valenzuela at work in the lab*

inadequate. "So the central question in all of our work becomes how we can make the adult nervous system grow and repair itself better," Dr. Fishman said.

A world leader in the field of neurobiology, Dr. Fishman has been trying to find the answer to that question for the past decade, first at the National Institutes of Health, and for the last eight years at the MGH.

Recently that work received a major boost when two Japanese companies awarded Dr. Fishman and the MGH a major research grant.

Sumitomo Chemical Company and Sumitomo Pharmaceuticals Company, both of Osaka, made the grant to the MGH after touring several other neuroscience laboratories in the U.S. The five-year, $4 million grant is for Dr. Fishman's work on proteins related to the growth and regeneration of nerve cells. Ultimately, the two Japanese companies hope the research will lead to the development of new drugs and treatments for people suffering nerve damage caused by stroke, injury, or diseases such as diabetes and Alzheimer's.

"The Japanese companies are taking a long-term view of a very difficult scientific problem — the understanding of basic nerve cell mechanisms," said Dr. Fishman, who stressed that many more fundamental questions have to be answered over a period of years before any treatment applications will be realized from the research.

But even though many questions still remain unanswered, much has been learned and accomplished in recent years, and much groundwork has already been laid.

For many years scientists have known there was a specialized cone-like structure at the very tip of a nerve cell that guided the growing nerve cell to its target. A major component of this "growth cone" is a protein called GAP-43 (Growth Associated Protein). This protein has been the focus of Dr. Fishman's investigation.

"Because there was so much of this protein in the growth cone, our assumption was that GAP-43 was important for the remodeling or repair of the nerve cell," Dr. Fishman said.

In laboratory experiments at the MGH and elsewhere, such as at McLean Hospital in the laboratory of Dr. L. Benowitz, scientists have accumulated evidence that this assumption may be true. They observed that the levels of GAP-43 gene expression went up when nerve cells grow. When the nerves reached their targets and stop growing, the levels of GAP-43 diminish.

Scientists then had to figure out how the GAP-43 knew where in the cell to go.

"That's no mean feat," Dr. Fishman said. "A single nerve cell is a very long cell; sometimes it will reach from the brain all the way out to the arm over many, many inches at least. Guidance of that kind of cellular traffic for a single molecule is not trivial."

In the laboratory, investigators found at least part of the answer — a single stretch of 10 amino acids on the end of the GAP-43 protein specifically designed as a "trafficking" device.

"If you get rid of that region from the protein, it no longer finds its way down to the growth cone," Dr. Fishman said. Conversely when scientists attached the stretch to another protein not bound for the growth cone, the protein would suddenly change course and go to the GAP-43 location instead.

"So now we know it's turned on at the right time and it's sent where it's supposed to go," said Dr. Fishman. "So then the next question becomes, 'Does it actually do anything once it's down there?'"

Although MGH scientists are still working on the answer to that question, preliminary indications are extremely exciting.

In an experiment conducted by Mauricio Zuber, PhD, a former MGH research fellow now on the faculty at Colorado State University, MGH scientists transfected (artificially introduced) the GAP-43 gene into fibroblasts (a flat cell found throughout the body especially in connective tissue).

Much to the surprise of the scientists, the fibroblasts in cell culture began to change their structure. The formerly round fibroblasts suddenly started to sprout fine little pointed filaments (filopodia) that looked remarkably like those of a growth cone. The GAP-43 infected fibroblast was not a growth cone, but the experiment caused great excitement in the laboratory.

"If we can take this one protein and generate something that looks a little bit like a growth cone in a fibroblast, a cell that doesn't have much of the specialized machinery of the nerve cell, maybe we won't need many other proteins to make a growth cone occur," Dr. Fishman said.

While GAP-43 is the major protein found in the growth cone, it is not the only one. Scientists now set out to isolate and identify the others and determine if and how they interact with one another.

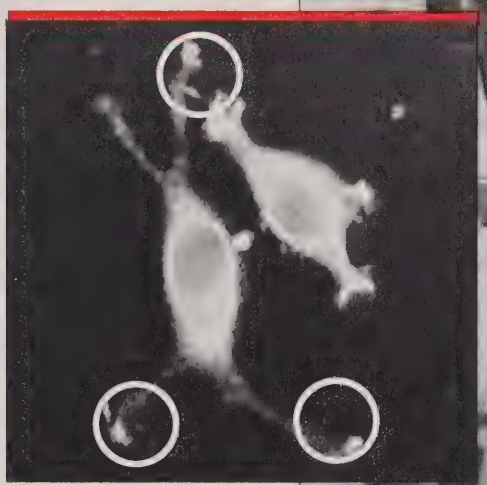
Stephen M. Strittmatter, MD, PhD, an MGH Research Fellow in Neurology, iso-

lated two of the other three major proteins in the growth cone. He identified them as subunits of $G_0$ — a member of the family of proteins called the G family.

Scientists already know several things about the $G_0$ proteins. Perhaps most important is the function they serve as links between cell-surface receptors and messenger systems within the cells.

"Their role is very important," Dr. Fishman said. "They sit on the membrane and basically couple between the outside of the cell and the inside of the cell."

But the $G_0$ protein could initially be activated only by receptors outside the cell — or so scientists thought. Dr. Strittmatter and Dr. Dario Valenzuela proved otherwise. In a test tube they mixed purified $G_0$ and purified GAP-43. The $G_0$ protein was provided by Dr. Eva J. Neer, Professor of Medicine at Harvard Medical School and biochemist at the Brigham & Women's Hospital. They then measured the activity of the $G_0$ protein.



*Two cells grown in tissue culture to resemble neurons are magnified about 1,000 times. Several "growth cones" (circles) are clearly visible extending from each cell. A protein found in the growth cone may hold the secret to nerve cell growth and repair, and is the focus of intense investigation by the MGH Medical Services Developmental Biology Laboratory.*

"We found the $G_0$ was more active when the GAP-43 was present than when it wasn't present," Dr. Strittmatter said. "We already knew that GAP-43 was in the growth cone. We already knew that $G_0$ was in the growth cone. And now we showed that they worked together in the test tube. So the conclusion was that they probably interact in the growth cone itself."

The conclusion was quite startling because it was the first time anyone had shown that $G_0$ could be activated by a protein within the cell structure.

The results of this MGH research, which were published earlier this year in the journal *Nature*, have been well-received and caused considerable interest within the scientific community.

To many, the research seems to hold out the promise of resolving the long-standing dilemma between cellular patterns of development driven by signals from both inside and outside of cells. How would a resolution of this conflict translate into benefits to people suffering irreparable nerve damage?

"If one could activate this signalling system from inside the cell, one that is usually activated from outside the cell, you have a way of setting the cell's sensitivity to its environment," Dr. Fishman said. "It could certainly be a way for an intracellur gene growth program to interact with all those influences from outside the cell that are known to affect growth."

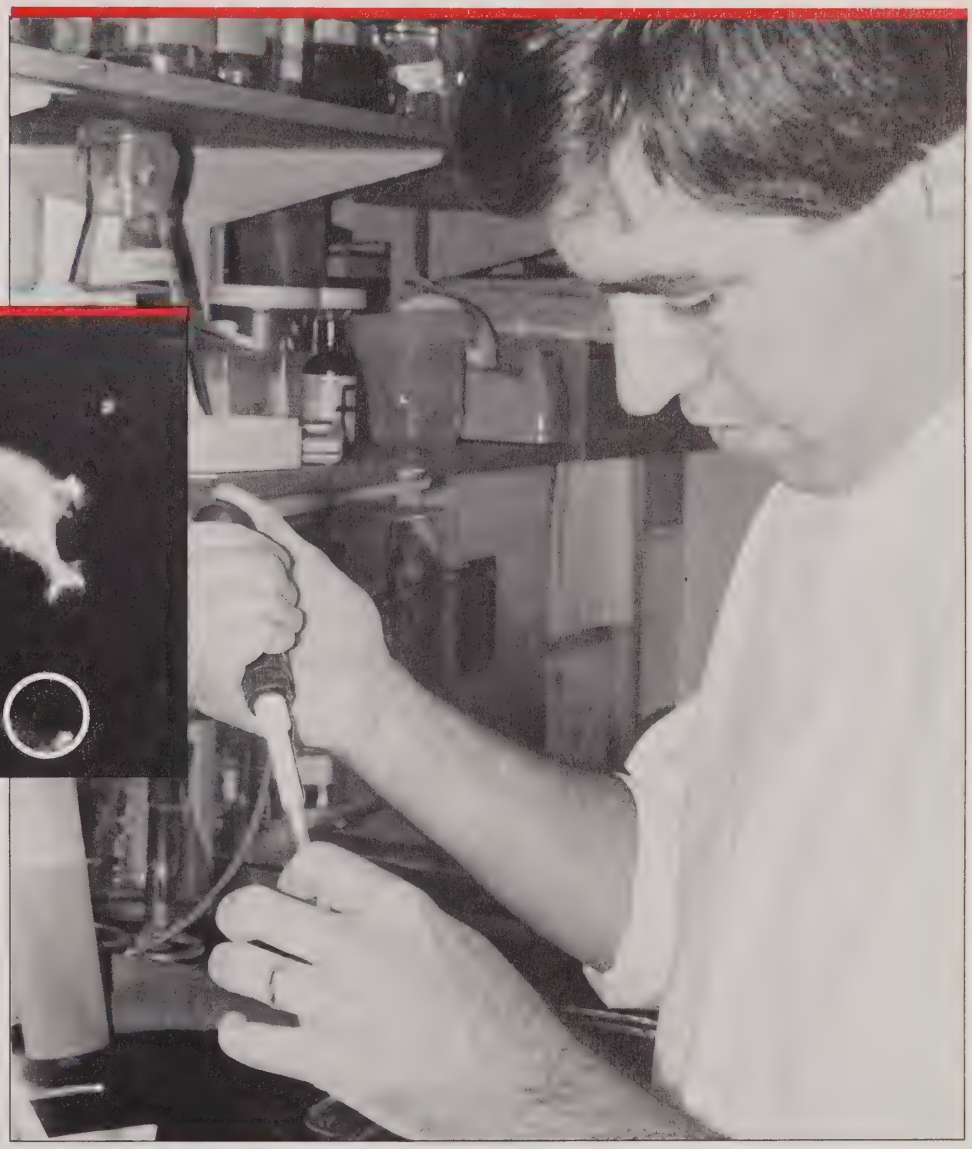
A test tube is a long way from a human being. There are many, many more questions that have to be answered and many, many more experiments that have to be carried out before any patient applications will even begin to be thought of.

But the work in the lab has been going well, and the recent Sumitomo support is a major boost to the effort. Of the 12 scientists who work fulltime in the MGH Developmental Biology Laboratory, about half are assigned to GAP-43 and related research. .

"It's a major commitment on the part of the lab," said Dr. Fishman, who is also an Associate Professor of Medicine at Harvard Medical School. "But it's gone well.

"At present we have little we can do for patients with spinal cord injuries. All that we would need is one molecule that would help just a little bit of growth get across that wound in the spinal cord. Even a small return of function would be wonderful.

"We're talking about desperate situations here. That lends an urgency to our work." ■



*Dr. Stephen M. Strittmatter separates proteins according to molecular weight in the MGH Developmental Biology Laboratory.*

# *Training Doctors the Old-Fashioned Way — Firmly*

THE YOUNG WOMAN who checked into the MGH in September was a patient with the kind of problem medical students read about in textbooks, cram for before finals, get tested on, and then usually forget.

After all dermatomyositis is not the sort of disease most physicians treat on a daily basis. "Once in a lifetime, maybe," said Dr. Karel Raska, a resident in internal medicine. "It's a very rare rheumatologic [any of a variety of painful disorders affecting the connective tissues of the body, especially the joints] syndrome [group of symptoms]. It's the kind of disorder you read about, but you rarely ever actually see."

But thanks to a new way of training doctors at the MGH, dermatomyositis is not only in the vocabulary of MGH interns, it is in their own personal repetoire of experience as well.

The Department of Medicine, under the direction of Dr. John Potts, has revamped the way it trains young doctors. Called the "Firm System," the new approach combines the MGH tradition of bedside care with a highly structured small group team approach to diagnosis and patient management.

"Under the old system only the intern and the medical resident assigned to that woman would have been exposed to her illness," Dr. Raska said. "The rest of the house staff likely would not have even known she was here.

"With the Firm System a whole group of interns and residents sit down with the Firm Chief and discuss the disease, and meet, interview, and examine the patient. So a larger group is exposed to her.

"One of the big advantages of training at the MGH is the number of patients with unusual disorders that we get here," Dr. Raska continued. "A big plus of the Firm System is that it gives more people exposure to them."

The MGH is the original and largest teaching hospital affiliated with the Harvard Medical School (HMS). Like most teaching hospitals, its postmedical school training program in internal medicine consists of three years — one year of internship followed by two years of residency training. The department also offers one-year internships to medical school graduates who will be pursuing training in nonmedical specialties such as neurology, psychology, radiology, and anesthesiology.

In recent years, however, mounting pressures on the medical profession have compromised the quality of teaching at many American institutions, including the MGH.

An aging, sicker population has meant more complicated care needs. Increased government and insurance regulation have meant shorter, more intensive hospital stays, more admissions, increased patient turnover, and more and more paperwork. Meanwhile, malpractice insurance rates have until recent months continued to rise along with the demands on physicians' time. Morale in the profession has declined.

About five years ago the MGH Department of Medicine responded to the rising numbers of admissions and more complicated patient care needs by boosting the numbers of interns. This increase in house staff (interns and residents) helped even out the workload, but added substantially to the teaching responsibilities of staff physicians.

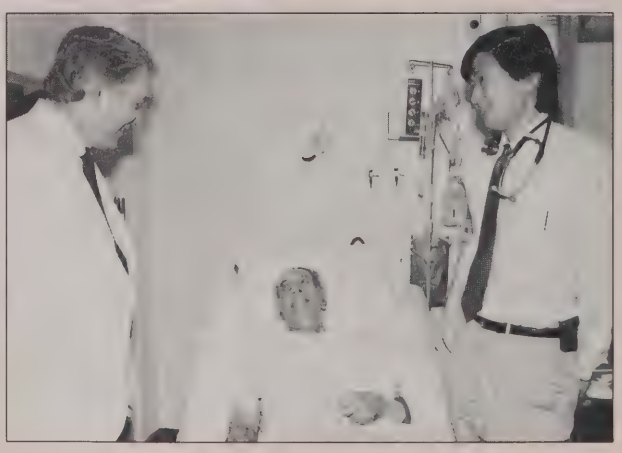
"We have many superb clinical teachers," said Dr. Lloyd Axelrod, one of the three new chiefs appointed to head the new Firm System. "But as the Medical Service expanded, the demands on our staff started to become overwhelming. We wanted to respond in a creative manner to those pressures; to reaffirm our excellence."

The Firm System responds to those pressures by dividing the Department of Medicine — the largest department at the hospital — into thirds. During their rotations through all the various services of the department as part of their postmedical school training, house staff are now assigned to a Firm. They then rotate on teams within that Firm.

A few services such as the Emergency Department, the Hematology-Oncology Floor, and the Intensive Care Units have been left out of the new system so that members of all three Firms will have the opportunity to rotate and train on these services and get to know their colleagues.

The crucial links in the new system are the Firm Chiefs — three highly talented and gifted teachers, whose primary responsibilities are patient care

*Dr. Lloyd Axelrod (center) conducts one of two weekly sessions with a group of interns and residents. The sessions are part of the new "Firm System" the Department of Medicine has adopted to train future doctors.*



*Dr. Axelrod (left), and resident Daniel Chung, check in on patient Robert Zambella during bedside rounds in the Baker Building before the unit was moved to the Ellison Building.*

and teaching.

The three Firms are named for former Chiefs of Medicine who also distinguished themselves as outstanding care givers and teachers. The James Howard Means Firm is headed by Dr. Axelrod, a member of the MGH Diabetes Unit and an Associate Professor of Medicine at Harvard Medical School.

The Walter Bauer Firm is headed by Dr. Leslie S. T. Fang, an MGH physician and Associate Professor of Medicine at HMS.

The James Jackson Firm is headed by Dr. Morton N. Swartz, the founder and for 34 years the Chief of the MGH Infectious Disease Unit and a Professor of Medicine at HMS.

Among them the three new Firm Chiefs have close to 75 years of medical experience. For Dr. Axelrod, in particular, his new duties complete a cycle of learning and teaching which began at the MGH in 1970 under Dr. Swartz, a former teacher now turned colleague.

"The people I revere the most in my professional life have been some of my teachers in medical school and residency," Dr. Axelrod said. "One of those who had an extraordinary impact on me was Mort Swartz. So it's particularly gratifying now to work closely with him."

All three Firm Chiefs — Dr. Axelrod, Dr. Swartz, and Dr. Fang — hold rounds twice a week throughout the year. About 10 people participate in the sessions, including four interns, two residents and three medical students. In addition the residents meet alone with the Firm Chief once a week to discuss patient care, review the literature, and engage in discussions of particular patient needs.

"In addition to their teaching role, Firm Chiefs are available as mentors and advocates for the house staff on their Firms," Dr. Potts said.

Other members of the staff also serve as mentors to the house staff, helping to orient new interns and ease their progress through the hospital.

"The mentoring program is particularly important to the Firm System by fostering better communication and support between staff and house staff," Dr. Potts said. "The mentor helps to welcome and orient new interns to the MGH, maintains close contact throughout residency, and follows their postresidency progress."

The Firm System with its emphasis on bedside teaching, mentoring, and smaller, more cohesive and intimate groups, accomplishes several objectives.

On the one hand the system provides more one-on-one teaching and interaction between staff members and house officers, while at the same time lessening the teaching demands on other staff members.

"We've made a major effort to identify a few people who have a strong interest and a talent for teaching," said Dr. Debra Weinstein, a former Chief Resident instrumental in helping to draw up the Firm System. "The result is we have a smaller group of attending staff physicians who spend more of their time teaching than in the past."

But this new reliance on a few for more of the teaching duties does not mean the rest of the staff is left out. Another key component of the Firm System is the "Firm Visit." Various attending staff are asked to spend three months a year — not necessarily consecutively — teaching on the different firms. "This makes for added consistency because the same people are on the service for several periods during the year," Dr. Axelrod said.

Although the Firm System has been in effect only a year, Dr. Potts said morale is already improving with the new teaching system.

"The Firm System has helped to improve morale by fostering better staff-house staff communication overall and by providing a smaller group atmosphere for clinical and social activities. That is especially helpful in a large teaching hospital.

"Ultimately, the Firm System may have an impact on retention and recruitment of physicians by further enhancing the sense of mutual support and collegiality that has long been such a great asset of the Medical Service," said Dr. Potts, who is also Jackson Professor of Clinical Medicine at HMS.

Although the Firm System is new to the MGH, it is an old idea — one that traces its roots to the British method of training physicians. In British hospitals, firms are divided by specialty and headed by a professor of an affiliated medical school. In the United States, other teaching hospitals have also adopted features of the Firm System, although each approach is unique.

"The basic principle at all of these places is that you're taking a large institution and breaking it down into smaller, more intimate, more manageable subdivisions to enhance teaching, camaraderie and interaction," Dr. Axelrod said.

"We're not reinventing anything. We're just reasserting our traditional excellence." ■

# When Children Get Headaches

CHILDREN with headaches — even very young children — deserve more credit than their parents and many physicians often give them when it comes to providing useful information about their symptoms.

"Adults too often dismiss what children are trying to tell them," said Dr. William D. Singer, a member of the MGH Children's Service, "but children can communicate quite well about a symptom if you let them. They can tell for instance whether the headache is a squeezing pain or a throbbing pain."

Knowing that the headache is a pressure or squeezing kind of pain, said Dr. Singer, would increase the suspicion that the cause was intracranial pressure due to a possible hemorrhage or a tumor. A throbbing or pounding headache, on the other hand, would normally rule out an intracranial cause.

Headaches are one of children's most common complaints. Chronic headaches make up a substantial portion of outpatient ailments treated by pediatricians.

But rather than asking the parent to describe the child's symptoms, Dr. Singer said pediatricians should question the child directly.

"With the older child this is not difficult to do," Dr. Singer told a recent "pediatrics update" conference sponsored by the MGH at Harvard Medical School. "His language skills are usually developed well enough for him to provide a quite complete description of his symptoms and even what might have caused the headache, such as what he had to eat or didn't eat that day."

For children older than 8 with good language skills, Dr. Singer recommends the child keep a daily diary of his headaches. In the diary, the child is asked to record such things as when the headache started, what it feels like, the last time he ate before the headache started, what he ate, what happened at school or at home that day, etc.

"Certain foods often precipitate headaches," Dr. Singer said. "Chocolate is one common example. Not eating is another. We're also looking for emotional issues. Is the child doing well in school, academically and socially? Are

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# — When Children Get Headaches

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there pressures at home? A divorce, an illness of a parent or a sibling? What was the child doing when the headache came on? All of this information is important when trying to diagnose and treat chronic headaches in children. And who better to tell you than the child himself?"

For the younger child whose vocabulary has not yet sufficiently developed, such detailed questioning about his headache is obviously not possible. But Dr. Singer said it is a mistake to ignore the child's input during an evaluation. Even very young children can provide important and useful clues about symptoms.

Dr. Singer said one of the best ways to elicit information from a very young child is to give the child a doll or a stuffed animal and ask him, 'What would give the doll a headache like you've got?'

"It's really very interesting to watch," said Dr. Singer. "A child as young as three will pound on the doll to indicate a pounding headache or squeeze the doll to indicate a muscle contraction. It's a very effective way of dealing with younger children whom you'd think because of communication problems would delay the initial diagnosis. But they actually do quite well."

Another useful strategy Dr. Singer uses in communicating directly with very young children is to put the doll in the child's lap and ask the child what he would do to his brother or sister to give them a headache.

"They usually get a twinkle in their eye when you ask them this," Dr. Singer said.

*Victor Rivera, 4, of Roxbury, MA uses a doll to act out his headache symptoms.*

Dr. Singer, who is also a staff member of Cambridge City Hospital in neighboring Cambridge, admitted that using a doll or a stuffed animal to communicate directly with a very young child usually just "gets you in the ballpark."

"You will probably have to do CT [computed tomography or CAT scan] or MRI [magnetic resonance imaging] anyway in any of these cases," Dr. Singer told the pediatricians attending the MGH conference. "But at least you're establishing communication with the children and they're showing you how they operate."

And Dr. Singer added there is another important reason for enlisting a child directly in his own health care.

"It says to the child, 'You are important. I respect you. What you have to say is important.' And that's an important message for any child." ■

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# Researchers Close in on Atherosclerosis

ONE OF THE MOST difficult questions Dr. Mason Freeman faces every day as Director of the MGH Cholesterol Clinic comes from the 40-year-old man with a cholesterol level of 240 who wants to know if a heart attack lies ahead.

"Right now we don't have a reliable way of answering that question," Dr. Freeman said. "All we have are a bunch of statistics that say he's at increased risk if he doesn't lower his cholesterol. But I can't tell him for sure he's going to have a heart attack."

But what if doctors could take that person and do a noninvasive test to determine how much plaque he has in his coronary arteries?

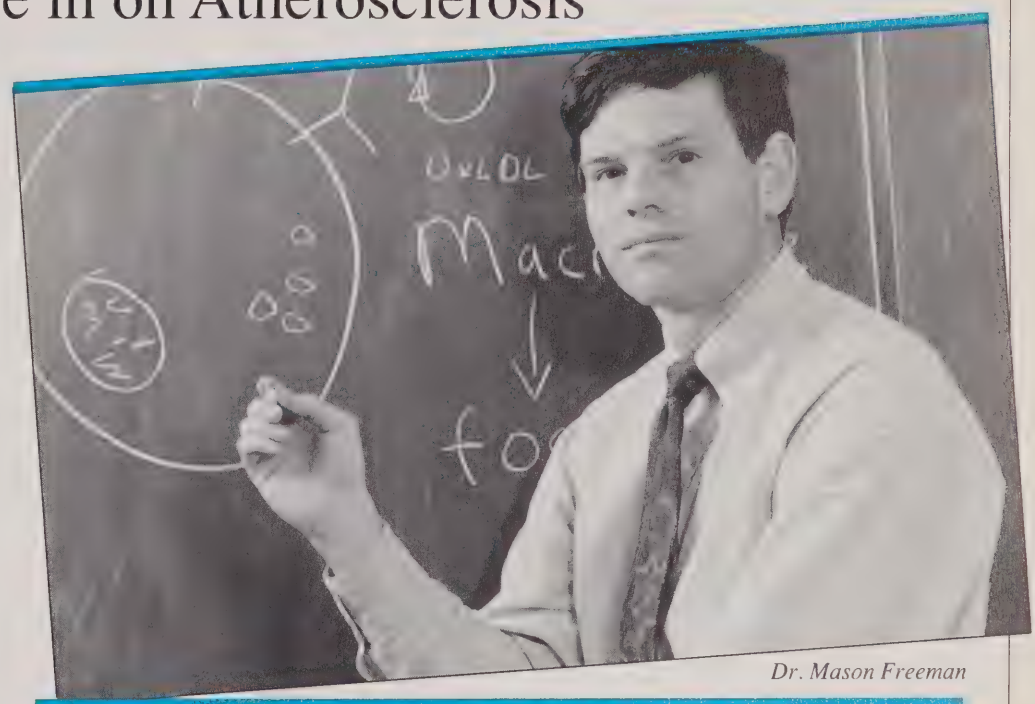
"If we could do that," Dr. Freeman said, "we would be able to give people an answer with near certainty about whether their cholesterol is something they should worry about."

Take heart, America, that day appears to have moved closer.

A laboratory discovery by a Massachusetts Institute of Technology research team that included Dr. Freeman may lead to just such a diagnostic test for atherosclerosis, the world's number one killer.

Atherosclerosis is a common condition in which the inside wall of the coronary arteries becomes thickened and clogged with lipids (fat or cholesterol). By narrowing the blood's passageway, these so-called atherosclerotic plaques that build

*(Continued on Page 6)*



*Dr. Mason Freeman*

## *Memories Pile Up on Frontlines of AIDS Epidemic*

EIGHT YEARS of nursing AIDS patients cannot erase the faces for Teri Flynn. And in eight years there have been so many faces to remember.

"Sometimes I'll be interviewing for a nursing position, and I'll ask the person if they've ever cared for an AIDS patient," said Ms. Flynn, RN, an AIDS nurse specialist.

"And they might answer, 'Yeah, back in 1985 I cared for John Smith.'"

"And I'll say, 'Really? I remember John so well.'

"I can't help it; I just remember them. I've gotten close to so many of them there's no way I could ever forget any of them."

On the frontlines of the AIDS epidemic, remembering is how nurses at the MGH cope.

For Ann Locke the memories are of an angry young man named Bob.

"He was a very angry fellow — angry at his disease primarily, but displacing it on everything and everyone," said Ms. Locke, RN, a psychiatric clinical nurse specialist. "His anger was so intense it made people want to withdraw from him."

When the staff nurses taking care of Bob became reluctant to enter his room, Ms. Locke was consulted.

"For some reason he and I made a connection," Ms. Locke said. "I was able to show him that his anger was something he was hiding behind. It took a long time, but he finally let a couple of nurses in. So at the end he gave himself permission to receive some nurturing."

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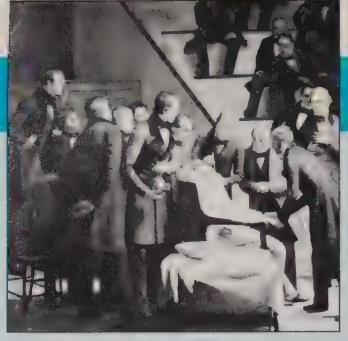
EDITORIAL

# When Disaster Strikes . . .



ON DECEMBER 12 an Amtrak train derailed and smashed into a commuter train beneath Boston's Copley Square area. More than 250 passengers suffered injuries. Fortunately, and surprisingly, only a tiny number had life-threatening injuries. Most, however, experienced confusion and fright at the scene, and some of the rescuers inhaled smoke while carrying out so well their missions.

Because of their large numbers, the injured were brought to seven Boston hospitals. With 99 patients, nearly 40 percent of the total injured, the MGH had by far the most. About 60 of the patients arrived simultaneously, a situation that compounded the difficulty. It was 9:10 a.m. when two full buses unexpectedly arrived 40 minutes after the crash.

Moments after that arrival, the hospital went into a full disaster plan. One way or another most departments of the hospital became involved. About 50 physicians not assigned to the Emergency Department were pressed into service within minutes. To provide necessary space, the main lobby, juxtaposed to the Emergency Department, was cleared of nondisaster traffic and became the triage area. Medical personnel first checked the patients there, decided the order of treatment based on severity of injury, and assigned the injured to the appropriate medical specialties. Behind the lobby's information desk, Medical Records set up a system to log in all victims.

In the adjacent Wang Ambulatory Care Center lobby area, the Social Service Department established a discharge desk for those treated and ready to leave. Another desk became the site of the communications network for families seeking news of their loved ones. Refreshments were provided for those family members. The hospital's Patient Care Representatives Office assisted with special needs: One newlywed husband was concerned because the list of patients being treated lacked his wife's name. It was only after a search for the maiden name that she turned up—not seriously injured.

Since 1942 the MGH has had a disaster plan. Only months later the hospital used the plan in the holocaust that was the Cocoanut Grove fire. From that year on, the MGH has modified the plan many times as buildings and technology have changed. Expertise and experience in dealing with disasters have been handed down from one generation to the next. That tradition has kept the MGH ready to cope quietly and effectively with whatever has been asked of it. ■

## — *Memories*

*(Continued from Page 1)*

For Sue Caloggero the memories are of a dear friend.

"When Lenny asked me to be his primary nurse, it was a very difficult decision," Ms. Caloggero, RN, said. "Before that I had gotten involved in the AIDS epidemic on my own in terms of trying to get myself informed and that kind of thing. But suddenly here was someone I knew and was fond of who had the disease and wanted me to be his nurse."

The year was 1986—still early in the epidemic—and few drugs were available.

Lenny was hospitalized often, each time on Baker 7 where Ms. Caloggero worked. He died the day after the AIDS Walk that June.

"It took me a long time to get over his loss," said Ms. Caloggero, who began taking on more AIDS patients and volunteer activities after Lenny's death. "It wasn't just a couple of activities and boom, everything's back to normal. It took a long time. I still think about him."

For Teri Flynn, the memories are of the cold January day she watched and prayed as a young man named Rob from New Hampshire died in the Emergency Department at the MGH.

"I'll never forget the feeling of aloneness I had," Ms. Flynn said. "I remember thinking how much fuss and excitement there is when a person is born. And now this young man in his 20s was leaving the world, and there was no one around to say goodbye. To die alone, I think, is just

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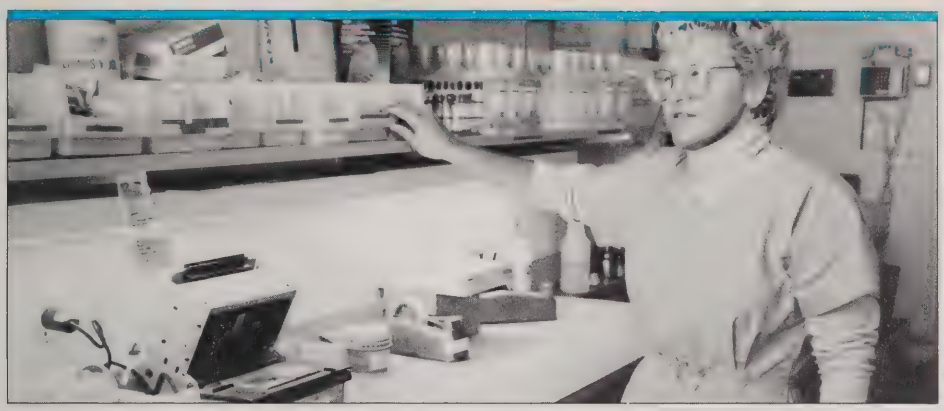


*For Sue Caloggero, RN, burying one wave of the AIDS epidemic was enough. After four years of AIDS care, Ms. Caloggero asked to be transferred to another floor of the hospital.*

so devastating."

The MGH admitted its first AIDS patient in 1982 and opened its AIDS clinic a year later. Today the MGH, through its inpatient and outpatient services and numerous drug study protocols, has seen its AIDS patient population grow along with the epidemic.

For the nurses who staff the hospital's AIDS clinic and the inpatient floors, theirs is an assignment of choice. "I never thought when I was in nursing school I would see an epidemic or see a new disease," said Ms. Flynn, the hospital's first AIDS nurse specialist in 1983. "I was involved not only in patient care but also in research. My office was right next to the research lab. It was all unique and very exciting. I wouldn't trade the opportunity to help these patients for anything."

Other nurses who have also chosen to work in the AIDS clinic or care for AIDS patients on the hospital's medical floors, echo her sentiments.

It is a small group of nurses that on the one hand says AIDS care is not any more difficult or different than caring for patients with other complicated, fatal diseases. On the other hand, these same nurses say AIDS care is *completely* different.

"It is the emotional piece of AIDS care which is the straw that shifts the balance," Ms. Locke said.

And that emotion, say the nurses, comes not from watching a patient die but from watching him live.

"In the Emergency Department nurses see death all the time, but they see it fast, sudden — an accident or a heart attack," Ms. Flynn said. "But we knew the person with AIDS when he was well. We know the name of his dog; we know his family; we know his life because he comes in once or twice a week. And when he's not coming in, he's calling us on the telephone, or his lover or family is calling us on the telephone. Care of the AIDS patient is all the time, all the time, all the time. It never stops."

Nurses and other health care professionals even have a name for this nonstop care: "Waves"— one wave of patients after another. "The first wave is over," Ms Caloggero said. "We're on the second wave now."

Eight years after the AIDS epidemic hit Boston, the disease is still fatal. Drugs such as AZT have helped slow the progression of the disease and improved the quality of life for patients but there is still no cure.

"When I reflect back to when I started here in 1983, I realize that all my friends, all my patients, and the rapport and emotions that were all tied up with them, are completely gone," Ms. Flynn said. "That's very difficult sometimes."

For Ms. Caloggero, burying one wave of the epidemic was enough. After four years of intensive inpatient AIDS care, she volunteered for another floor of the hospital. "I can name 10 or 15 of those guys that I knew or took care of who are all gone now. After a while you just bury too many people. It's one of the most draining experiences; it pulls out everything."

But even as the casualties continue to mount on the frontlines of the AIDS epidemic, so does hope.

"From 1983 to 1985, everybody was dying," Ms. Flynn said. "As nurses the most we could do was give comfort and support. But now I see AIDS patients living longer. I'm giving them medications that can improve their quality of life for a period of time. That's important for some people who really need to get some things done before it's their time to die. And I'm hopeful that through our research and care some people will be able to live even longer with AIDS.

"I feel good about that and take a lot of support from that."

And from her memories. ■

*Teri Flynn, RN, monitors the blood pressure of AIDS patient Bill Franklin of Cambridge, MA.*

## Physical Therapy at 50:

# Many Challenges Lie Ahead

*Stella Prevost, Coordinator of Pulmonary Rehabilitation, monitors Jack McFadden's progress on an exercise bicycle. Ms. Prevost designed an exercise program for Mr. McFadden of Dorchester, MA, following successful surgery to remove part of his lung.*

PHYSICAL THERAPY, a profession that was born on the battlefields of World War I, cut its teeth on a polio epidemic, and blossomed with a fitness craze, turned 50 this fall facing something of a mid-life crisis.

Several dozen friends, former patients, and alumni gathered November 16 at the MGH to celebrate the founding a half century ago of the Rehabilitation Physical Therapy Department at the MGH, and 30 years ago of the Cardiopulmonary Physical Therapy Department.

And while the twin milestones were an occasion for rejoicing and reminiscence, it was also a time for reflection on the many challenges that lie ahead for physical therapy in general and the MGH in particular.

Among the challenges facing the profession in the coming decades are the rising number of clinicians moving to private practice, the lack of research, and the role of the physical therapist in the acute care hospital environment.

*MGH health care workers provide iron lung respiratory care to paralyzed patients during the 1955 polio epidemic. The epidemic created an overnight demand for physical therapists.*

"We are facing one of the most exciting and challenging times in the history of PT," said Colleen Kigin, Director of Physical Therapy Services at the MGH. "We have some tough issues ahead."

As a profession, physical therapy in the U.S. is still largely rooted in the musculoskeletal, neuromuscular emphasis that developed out of the rehabilitative needs of World War I veterans. That focus also dominated early care at the MGH.

Dr. Arthur Watkins, a neurologist on staff at the MGH, was given the task of starting the Physical Therapy Department 50 years ago. He successfully recruited Mary Nesbitt to return to the Boston area from Buffalo, NY. Ms. Nesbitt was a graduate of the Harvard Medical School/ Children's Hospital Physical Therapy program (now the Simmons College Physical Therapy Program) and later became the President of the American Physical Therapy Association (APTA) from 1954-56. Thus began a long tradition of leadership at the MGH in the profession.

In 1955 the U.S. polio epidemic changed the practice of PT almost overnight. The disease, which is associated with a degeneration of cells in the central nervous system, struck almost 29,000 Americans, killing nearly half of them. The epidemic created a huge, immediate demand for physical therapists experienced in caring for patients not only with the physical paralysis but also with the respiratory difficulties associated with the disease.

After the polio epidemic subsided, however, interest in providing pulmonary care waned. PTs in many U.S. hospitals, including the MGH, went back to their earlier neuromuscular and musculoskeletal focus, leaving a vacuum that spawned the birth of a new profession called "oxygen" or "respiratory" therapy.

In 1960 the arrival from Finland of Ms. Mica Rie — one of the first chest physical therapists in the United States— rekindled interest in pulmonary care for physical therapists at the MGH, and the Chest Physical Therapy Department started. Chest PT is an interest that has since become a major focus of physical therapy at the MGH and now includes rehabilitation programs for the heart and lung transplant patients as well.

Two years ago the two hospital-based therapy departments (Cardiopulmonary and Rehabilitation) merged into one department. PT now consists of three services: Cardiopulmonary, Inpatient Rehabilitation, and Outpatient. Some 65 staff members are divided among the three services.

If the polio epidemic helped create an overnight demand for PTs in 1955, the American fitness craze has fed the demand ever since.

Orthopedic and sports injuries now make up half of the patient population in PT clinics across the country. At the MGH more than 80 percent of the outpatient population have orthopedic or sports injuries.

But even as the profession has grown, so have the arguments over techniques to treat the many populations receiving physical therapy.

"There are tons of arguments about techniques," Ms. Kigin said. "It's one of our real problems. We have grown up with clinicians developing techniques, but

have too little controlled research that these techniques are based on."

To address this problem the APTA formed a separate organization to raise funds for and support research in physical therapy. Expanding research activities is also a major goal for the MGH PT Department. Several major projects are already underway, including a study on irregular heartbeats in conjunction with Dr. Brian A. McGovern of Cardiology and two joint projects with the Departments of Orthopaedics and Neurology.

"All of the projects are focusing on what I consider the right questions: Does clinical intervention in PT make a difference for a particular patient group or population, and if so, how and how much?" Ms. Kigin said.

Increasing the emphasis on research in the coming years may also help solve another major problem for the profession — the competition of other practice possibilities, including private practice, over acute care hospital practice.

Twenty years ago more than 50 pecent of all PTs were hospital based. Today that number is 44 percent. At the same time the demand for physical therapy in the hospital setting has steadily risen.

Ms. Kigin attributed the exodus of practitioners to other practice sites to several factors. "I think as a profession we lost our focus on the acute care practitioner," Ms. Kigin said. "A number of students felt they should only work in a hospital for a year or two to get up to speed and then go into private practice; hospitals thought they could run departments with all new grads; the professional organization lost sight of the possibility for PTs to have meaningful careers in an acute care hospital. It really was multi-factorial."

The solution is also multi-faceted, Ms. Kigin said. It centers around offering the hospital as a career alternative. To accomplish this objective, Ms. Kigin advocates better compensation for hospital PTs, a "career ladder" for the advanced or expert clinician, more direct PT involvement in developing the physical therapy treatment and intervention, and more research opportunities. "The acute care setting is ideal for research," said Ms. Kigin, who is also a member of the Board of Directors of the APTA. "I think the need for research and the need for career laddering in the hospital setting can really dovetail and help solve each other."

Recently the MGH approved a new policy giving PTs at the hospital more autonomy. Previously every patient wishing to see a physical therapist had to be referred by a physician. The new policy enables some outpatients to see a therapist directly without a physician referral, although a close working relationship with physicians is maintained.

"It adds to our responsibilities, but we're very excited about it," Ms. Kigin said.

The policy shift for the hospital department follows formation of Physical Therapy Associates. PT Associates, which opened in 1988, is the first non-physician practice in the hospital's Professional Service Corporation. Its goals are closely integrated with the MGH PT Graduate School and the hospital-based department. The practice has attracted nationwide attention as an organizational model for attracting skilled practitioners to the hospital setting.

Another challenge facing PTs in coming years is the increasing pressure to specialize. Adapting educational and training curriculums are also at issue.

PTs graduate as "GPs"— general practitioners — able to handle everything from cerebral palsy to tennis elbow. Five years ago the APTA, recognizing the growing trend by clinicians to focus their practices in "specialties," began offering certification exams.

Although there are currently only 197 board-certified PT specialists in the country, Ms. Kigin foresees the day when most PTs will be board certified.

"At this point specialization is new enough to PT that many institutions have not required board certification to fill targeted specialty positions, but that is changing quite rapidly," Ms. Kigin said, noting the MGH is already seeking individuals with board certification for some of its positions. Currently the MGH has clinical specialty positions in cardiopulmonary, neurology, and orthopedics.

The increasing move toward specialization will also challenge the traditional notions about educating and training PTs. Currently patient care experience is incorporated into the educational process, lasting anywhere from a few weeks to six months.

"That's not a great deal of clinical experience when you graduate," Ms. Kigin said. "There are people, and I'm one of them, who are trying to foster discussion about moving toward a true internship like the medical model."

A significant event in the development of physical therapy at the MGH was the opening 10 years ago of the Institute of Health Professions, which includes a graduate program in PT. Many people contributed to the development of the IHP, including Nancy Watts, a physical therapist and the Institute's first acting Provost (1978-79). Today the collaboration between the hospital-based PT department and the IHP remains strong. Currently 7 members of the department are graduates, 10 are enrolled parttime, and 5 hold academic appointments.

In 50 years at the MGH, physical therapy has seldom had a dull moment. And with all of the work still left to do, it seems certain the next 50 years should be at least as eventful. ■

*Colleen Kigin, Director of Physical Therapy Services at the MGH, monitors Annette Ballem's blood pressure. Ms. Ballem of Londonderry, NH, who suffers from chronic obstructive lung disease, was working out under Ms. Kigin's supervision on an upper extremity ergometer.*

## — *Atherosclerosis*

*(Continued from Page 1)*

up can lead to strokes and heart attacks.

Scientists have long known that the process leading to atherosclerosis begins with the presence of a "foam cell" — a cell (macrophage) of the immune system. The macrophage enters an artery wall and becomes so loaded with cholesterol that the cell begins to take on a foamy appearance when seen under the microscope.

But how the cholesterol gets into the macrophage has long baffled scientists.

After four years of intense scientific sleuthing, the M.I.T. group and Dr. Freeman have isolated and cloned (reproduced) the gene which encodes the protein they believe responsible for that process — the so-called "scavenger receptor."

To understand the significance of the discovery, it is first important to distinguish between the two kinds of low-density lipoprotein. LDL is the major cholesterol-carrying particle in the bloodstream. Modified or oxidized LDL is found in atherosclerotic plaques.

Regular LDL is taken up (brought inside the cell) where it is broken down into its constituent parts by a protein called the LDL receptor that sits on the surface of the cell. The LDL receptor, however, does not recognize modified LDL. The scavenger receptor does.

Unlike the LDL receptor, however, which is very carefully regulated and takes up only as much LDL cholesterol as the cell needs, the scavenger receptor is not regulated. The more modified LDL presented to a macrophage, the more the scavenger receptor will take up and the more will be stored in the macrophage.

"The process of taking up modified LDL appears to be crucial to the process of making an atherosclerotic plaque," Dr. Freeman said. "And we've identified a molecule in cells that's responsible for taking that up. That's why we think this discovery may be so important in atherosclerosis."

The scavenger receptor cloned by Dr. Freeman and his colleagues was first identified 11 years ago by two investigators who met and trained at the MGH. Drs. Michael S. Brown and Joseph L. Goldstein now of the University of Texas Southwest Medical Center at Dallas, who won the 1985 Nobel Prize in medicine for their discovery of the LDL receptor, identified the presence of the scavenger receptor in 1979. A postdoctoral fellow in their lab, Dr. Monty Krieger, became interested in the scavenger receptor while working in Texas and decided to pursue studies of the protein after moving to the M.I.T. faculty.

Dr. Krieger's team of six investigators spent more than four years tracking down the elusive receptor. Most of that time went to purifying enough of the protein to determine the sequence of its amino acids.

Dr. Tatsuhiko Kodama, a former M.I.T. research fellow now on the faculty of the University of Tokyo, purified the receptor from the tissues of cow lungs. After extracting material from some 2,000 cow lungs, Dr. Kodama identified 19 of the 453 amino acids that make up the scavenger receptor's linear sequence. Nineteen, however, proved more than enough.

"Since there are 20 different amino acids, the possibilities of another protein existing with the same 19 amino acids in a row is extremely remote," Dr. Freeman said. "So when we knew the sequence of those 19 amino acids, we knew something that uniquely characterized the scavenger receptor."

Armed with those 19 amino acids, researchers were then able to determine the DNA sequence that would encode (convert) them. Once they knew the DNA sequence they could use the power of gene-cloning technology to isolate the full length receptor in the lab.

The scientists actually cloned the gene in May of 1989. They reported the discovery in February last year in an article featured on the cover of the prestigious scientific journal *Nature* .

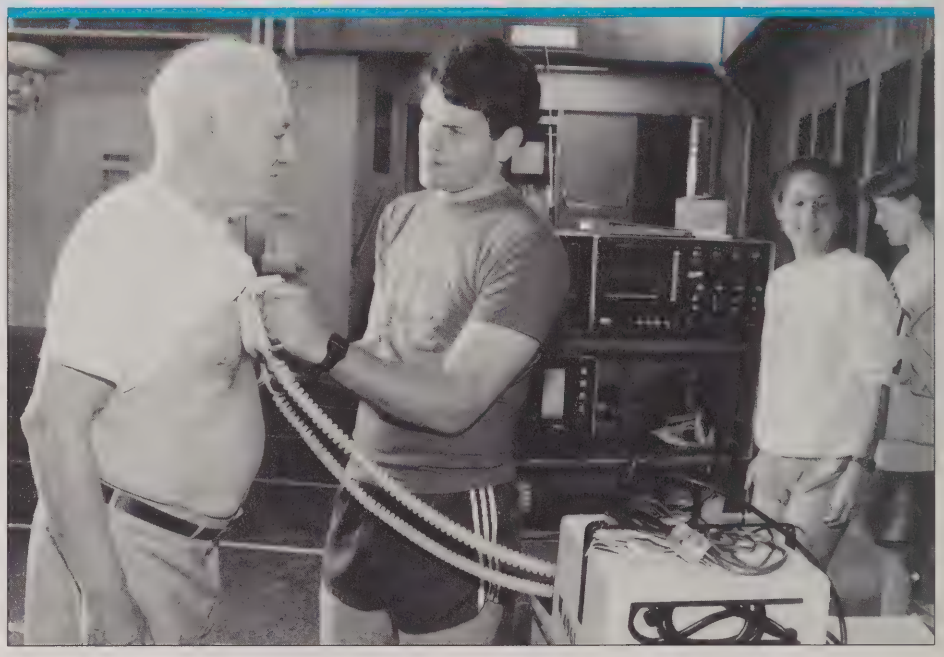
Drs. Brown and Goldstein editorialized in the same issue that the finding may provide a key to atherosclerosis.

"The discovery means that now we can take the receptor and put it in a cell that doesn't normally have it," Dr. Freeman said.

In laboratory experiments researchers have already done that.

"By giving cells a receptor that they don't normally have, we've been able to load the cells with modified LDL cholesterol," Dr. Freeman said. "Assuming there aren't other scavenger receptors we don't yet know about and haven't cloned, our receptor is almost certainly playing the role of converting the macrophage in the artery wall into the foam cell. Without the scavenger receptor, presumably the macrophages won't become foam cells because they don't have any way of getting large amounts of modified LDL in."

More laboratory experiments must be carried out before scientists will know everything they need to know about this



***Above:*** *Dr. Freeman monitors the heart rate of a patient who has just completed an exercise workout.*

***Below:*** *A three-dimensional computer model of how scientists think the scavenger receptor looks based on its linear sequence of 453 amino acids. The model appeared on the cover of the February 8, 1990 issue of Nature.*

complex disease and the role of the scavenger receptor. But Dr. Freeman said a possible patient application is already on the foreseeable horizon.

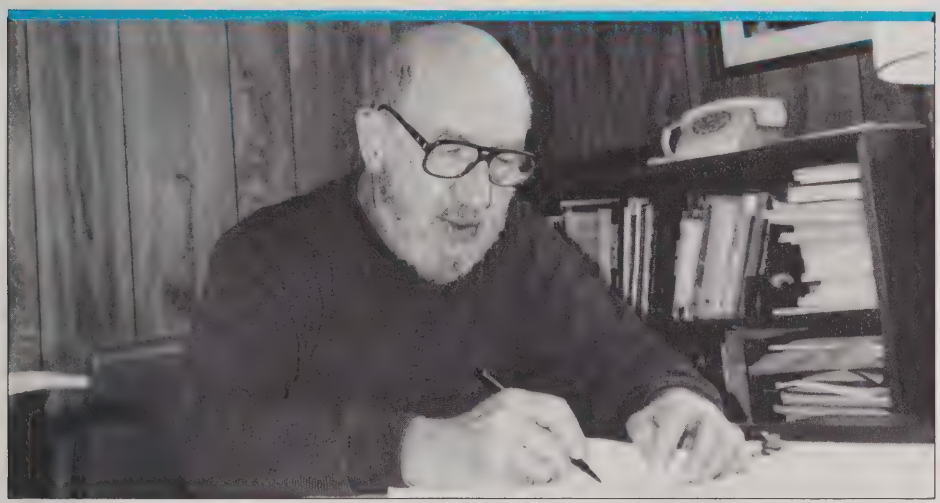
Currently he is trying to develop a diagnostic test for atherosclerosis that would determine the buildup of macrophages in the artery wall.

"The macrophages are not normally present in a clean pristine artery wall, but when you get an atherosclerotic plaque, they're present in enormous amounts," said Dr. Freeman, who is also Director of the MGH Cardiovascular Health Center. "Now here's a receptor that's expressed more or less explicitly on macrophages. If we could come up with a test that uses these observations to determine the extent of atherosclerotic plaques, it would be of great benefit to patients."

But Dr. Freeman cautioned that the disease process is not complete just because macrophages are congregating in the artery wall and forming foam cells.

"That's not the end of the story," Dr. Freeman said. "A foam cell is not an atherosclerotic plaque. The next question is how does a foam cell lead to this conglomeration of material inside an artery? Well, 16 other things probably have to happen after that. And each one of those things will likely be affected by at least one other protein.

"That's what makes these chronic diseases like atherosclerosis so challenging for scientists and doctors." ■



*Dr. Avery D. Weisman at work in his office*

# *Retired MGH Psychiatrist Helps Pet Owners Cope With Loss*

DR. AVERY D. WEISMAN knew he was on the right track when a former staff member asked him how he was spending his retirement.

"He wasn't what you'd call the most communicative person," said Dr. Weisman, the former Chief of the MGH Psychiatric Consultation Service who retired from the MGH in 1984. "But when I told him I was doing some volunteer work with people who had recently lost a pet animal, he suddenly wanted to talk. He told me about a cat he had lost seven years ago. And as he talked he began to cry. I realized that that was the first time he had acknowledged his grief."

Two years ago Dr. Weisman says he would have been surprised at such a display. Today he has to keep reminding himself he is not embarking on a new career.

Ever since the senior MGH psychiatrist and pioneer in the study of thanatology — the study of death, dying, grief, and bereavement — decided to extend that interest into pet loss, he has been constantly surprised at the response.

"Not having known too much about this area of grief, I didn't know what to expect," Dr. Weisman confessed. "But the animal-human bond is unique — it's genuine; it's primitive; it's archaic; it's authentic, and I have a great deal of respect for it. I've learned a lot from the experience."

Anyone who knows Dr. Weisman knows his great love of learning and of people have always marked his career. The principal investigator for Project Omega, a long-term study of people with cancer, and the author of three books on death and dying, Dr. Weisman was anxious to continue that interest in his retirement.

A great animal lover and longtime supporter of the humane society, Dr. Weisman decided to offer his services to the Animal Rescue League of Boston.

"We were quite excited," said Arthur G. Slade, president of the Animal Rescue League. "People become so attached to their pets, especially the elderly whose pets may be their only contact with another living thing, that when the pet dies, it's like losing a family member. It's very hard for many people to deal with that loss."

In cooperation with the animal shelter, Dr. Weisman ran an ad in a local paper offering free consultation in pet bereavement. "At first I was surprised at all the calls," Dr. Weisman said. "Now I'm not."

People from all walks of life, from age 20 to age 80, have called him. "The younger the person, the more apt to come in because the pet died a violent death," Dr. Weisman said. "Most older people have had their pets 15 years or more."

The grief people feel for a dead pet, Dr. Weisman said, can sometimes be more intense than for a dead parent or family member.

"I had a woman who lost her dog and her brother about the same time," Dr. Weisman said. "It was hard to tell if she was grieving more for the dog or the brother. I know that sounds strange but perhaps a little less so when you reflect that the dog had been her sole constant companion for many years."

Another young woman who came in for counseling after losing her dog, described the animal as her "closest relationship" since childhood.

"About three months later I happened to run into her — big smile on her face — at the shelter," Dr. Weisman said. "She said she had another dog. Then without losing the smile she told me her father had died."

Still another woman who lost her dog of many years had been married three times during the dog's long life.

"There was no doubt the woman had been closer to her dog than to any of her husbands," Dr. Weisman said.

Yet another woman visited her pet's gravesite and said daily prayers for him for six months.

One of his more unusual patients was a Buddhist priest who had kept five cats. "He was still grieving for one of the cats but fully expecting that one day he would discover the reincarnation of his lost cat

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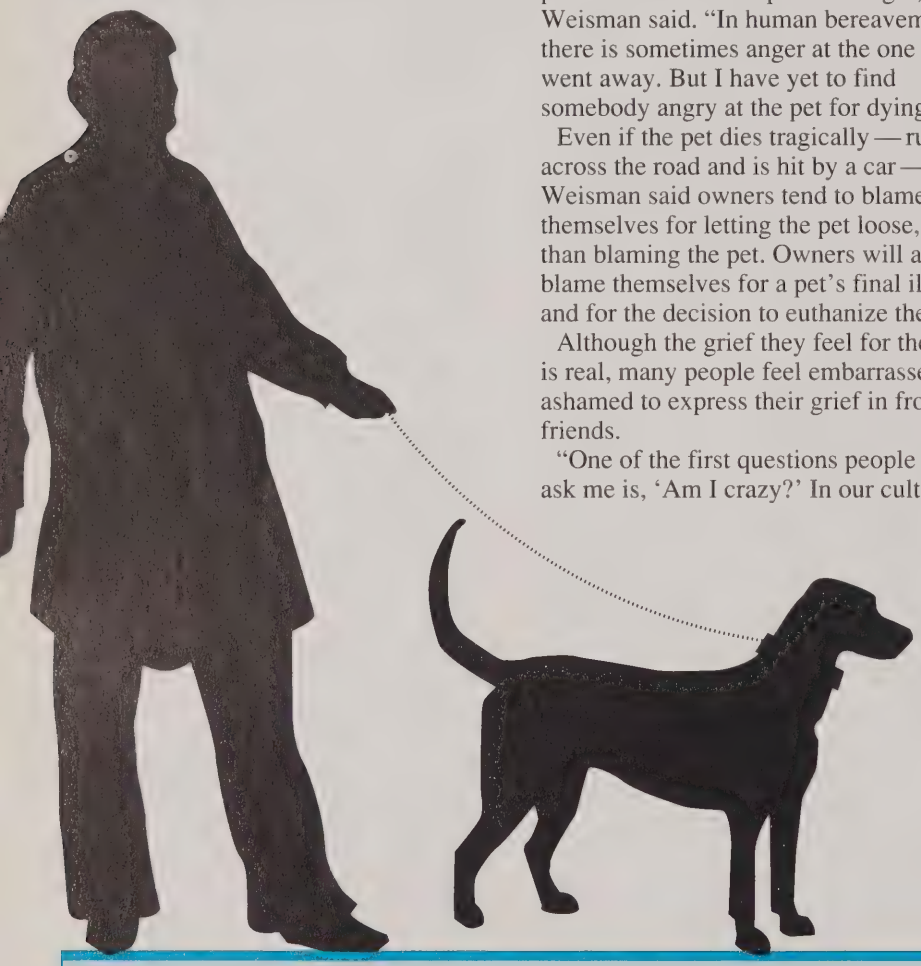
## — Pets

*(Concluded from Page 7)*

in some other animal or some other person as his religion teaches," Dr. Weisman said. "I found that belief to be an effective way of coping with loss, and not unlike what some people do when they lose a loved one. They may not see the loved one again in this life, but they do believe they'll see the loved one in another life."



Dr. Weisman has noted many other similarities between human and pet bereavement, including pain at having to give up things such as a food dish, a leash, or a collar that symbolized the pet. Grieving pet owners also say they frequently experience flashbacks about the dead pet, or see a shadow or hear a noise and think it's the pet. Most carry pictures of their pet.

"All the symptoms of human grief are present with the exception of anger," Dr. Weisman said. "In human bereavement there is sometimes anger at the one who went away. But I have yet to find somebody angry at the pet for dying."

Even if the pet dies tragically — runs across the road and is hit by a car — Dr. Weisman said owners tend to blame themselves for letting the pet loose, rather than blaming the pet. Owners will also blame themselves for a pet's final illness and for the decision to euthanize the pet.

Although the grief they feel for their pet is real, many people feel embarrassed or ashamed to express their grief in front of friends.

"One of the first questions people will ask me is, 'Am I crazy?' In our culture the only extended bereavement that's acceptable is for someone related to you."

When people do try to express their grief to others, Dr. Weisman said, they often feel foolish.

"One man I saw wrote an essay about his love for his dog and read it to his bridge group. The response was utter silence, embarrassed silence." Other people report similar experiences.

Dr. Weisman, who sometimes counsels people over the telephone if they cannot come into the shelter, does not give out advice about pet adoption. He says that is a decision people have to make on their own. "Some people believe getting another pet will relieve their depression; for others it's a sign that their depression is over. It's really up to the individual. But I personally believe the latter. I think it's better to be cured first — if one dares speak of bereavement as a cure — and then start a new relationship."

Although a few books have been written on the subject of pet bereavement, Dr. Weisman said he knows of no extensive research in the field.

"There are a lot of opportunities for research," he said. "I wonder for instance about the relationship of pet loss to psychosomatic symptoms or about pet loss and hospital admissions for depression. There are all sorts of questions that could be asked and investigated.

"This whole field is like unexplored land. Psychiatrists knew about it but didn't talk about it very much. It certainly has been a revelation to me, a brand new world."

A brand new career? he is asked.

"I don't want another career. I'm retired."

But he would like another dog. ■

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*When a Parent Dies ...*

# What Happens to the Children?

PRELIMINARY findings from a four-year study of school-age children after the death of a parent show that as many as one-fourth of them are having significant trouble adjusting to the loss.

A 1989 survey by the Institute of Medicine, part of the National Academy of Sciences, found that about 12 percent of all school-age children may go on to develop a behavioral or emotional disorder. For bereaved children, say the MGH Child Bereavement Study's authors, the risk could be as much as doubled.

"The majority of children who lose a parent manage very well," said Phyllis Silverman, PhD, a Professor at the MGH Institute of Health Professions and co-investigator of the MGH Child Bereavement Study. "But we still have to be concerned for a population of these children that is beginning to emerge where the risk of developing a serious emotional problem appears to be about double what it would be in the normal population."

The study also revealed that how well a child adjusts to the death of a parent may depend on how strong a "connection" to the deceased the child constructs and maintains. As one 10-year-old girl interviewed for the study said: "It's better to remember and share it with someone than to try and forget."

Nationally, one out of every 20 children will lose a parent to death before the age of 15. The Child Bereavement Study is surveying 125 of these children from 70 families in Greater Boston. All of the children are being interviewed at 4-month, 12-month, and 24-month intervals after the parent's death. To date all of the one-year interviews have been completed and investigators are nearing the end of the final interviews.

Dr. J. William Worden, an Associate Psychologist in the MGH Department of

*(Continued on Page 2)*

INSIDE

Flatfeet Do Not Have to Be Painful
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# *Transplantation Unit Takes Center Stage*

## Noted Researcher Coming "Home"

IN 1970 Dr. David H. Sachs was a second-year surgical resident at the MGH with a choice to make: Stay at the MGH and finish his surgical training or take a two-year research appointment at the National Institutes of Health.

Dr. Sachs took the two-year appointment.

"One thing led to another, and now it's been 20 years at the NIH," Dr. Sachs laughed recently.

This spring Dr. Sachs will finally end his "leave of absence" and return to the Surgical Service of the MGH — not as a third-year resident but as the first Director of the hospital's new Transplantation Biology Research Center in Charlestown.

The long-delayed homecoming also

*(Continued on Page 4)*

## "Father Figure" Changing Roles

LEADING transplantation surgeons and researchers from around the world gathered in Boston late last year to pay tribute to Dr. Paul S. Russell, recently retired as Chief of the MGH Transplantation Unit and one of the great "father figures" of the field.

"We had the entire history of transplantation in one room," said Dr. Robert H. Rubin, Chief of Infectious Disease for Transplantation. "It really was a testament to Paul's stature and contributions to the field. He is one of the real pioneers in organ transplantation both scientifically and clinically — a true father figure."

The glittering international conference, which will be preserved in a special edition of the scientific journal *Transplantation Proceedings*, capped off a

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EDITORIAL

# The Scars of War

FOR ALL but the deranged and morbid, war ***is*** hell. Those who fight certainly know. So do civilian populations who see missiles streak through the night sky. To the medical professions fall the task of healing the injured. It is never pleasant to view the carnage of young soldiers, their bodies torn open by shrapnel or charred by fire. Now we have the ability to heal many wounds and burns that once killed. Significant numbers of the seriously wounded will be able to return to meaningful lives.

The psychological scars of war can also be devastating: whether it's to a 3-year-old girl forced to put on a gas mask amid wailing sirens. . .a 27-year-old POW tortured by the enemy. . .or those veterans of Vietnam who endured physical and psychological torture then experienced the final trauma of insult when they returned home. . . . Still, much has been learned about treating the psychological degradation that has its roots in war. Lessons taught by the past give hope that psychiatric consequences can also be better treated. That seems to be so for many of those terrified by what is sometimes called battle fatigue.

The MGH learned to care for the military during the fratricide of the Civil War. In World Wars I and II the MGH established base hospitals on foreign soil. When the MGHers returned from war, they were often better professionals and more understanding human beings. Yet another war has brought a new generation of MGH caretakers to the horrors and nightmares of the battlefield. A number of MGH reservists have been activated, and other employees have enlisted. Like many teaching hospitals the MGH has also accepted the role of backing up the military and veterans' hospitals which will treat those savaged by war. Aiding countrymen injured after heeding the government's call to arms is a responsibility of the healing professions. The MGH has also pledged to treat the victims of disasters such as earthquakes. Indeed, as this space has noted, MGHers have, in addition to a variety of other missions of mercy, treated burn patients in operating rooms in the Soviet Union and brought back for care children deformed by the 1988 Armenian earthquake.

Natural catastrophes are unavoidable. As a democratic nation, our philosophical aim is to avoid war. In an imperfect world avoiding war is not always easy or even possible. Wars basically arise from man's inability or desire not to resolve problems peacefully. To some degree we perhaps all harbor a dark side that finds elements of war exciting. Fear of loss of life for ourselves and our loved ones helps to control this primal reaction. The football fan who loses himself in the excitement of seeing the opposing team's quarterback battered by a vicious tackle knows that feeling. It represents the release of anger and hostility from the volcano that is our own lives. From that viewpoint war is the ultimate catharsis. And until we all find civilized ways to release anger and hatred and to resolve problems, the bodies of young people will continue to be torn apart on the battlefield. ■

## — *Child Bereavement*

*(Continued from Page 1)*

Psychiatry and co-investigator of the MGH study, said the goals of the study are threefold. Investigators want to describe the impact of a parental death on schoolage children, identify "at risk" children, and develop an instrument that will identify these children at an early stage in the bereavement process.

Although a definitive portrait of the "at risk" child has not yet been drawn, clues are beginning to emerge from the early data.

One of the key differences investigators hypothesize between the well-adjusted child and a poorly adjusted one relates to the child's ability to maintain a "connection" to the deceased. Dr. Steven L. Nickman, an Assistant in Psychiatry in the MGH Department of Psychiatry and the psychiatric consultant to the Child Bereavement Study, described this phenomenon as "construction of the deceased." A paper on this topic presented by the authors at the annual meeting of the New England Council of Child and Adolescent Psychiatry won an award as the best "working paper" of 1990.

"The literature has been full of the importance for children to let go of the past," said Dr. Silverman, an Associate in Social Welfare in the MGH Department of Psychiatry. "But the people who argue this are the ones who have studied therapy populations."

"We've found that it's really very important for the child to construct a sense of this parent in his life." said Dr.

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PHOTOGRAPHS: Pages 5, 6, Stephen R. Smith, MGH Telesurgery Department; Pages 7, 8, Linda Goodspeed. Illustration Page 1, Arch MacInnes.

Worden, who is also a Lecturer on Psychology at Harvard Medical School.

The authors said the image a bereaved child forms of a dead parent will change over time as the child matures.

"The child of six may have a picture of his Dad as someone who threw balls at him," Dr. Silverman said. "By the time he's 16 and sees a picture of his Dad smiling, he may think, 'Oh, he must have been very happy that day.' He now has a sense of that person as a fuller human being. So the relationship will change as the child changes and that's good."

A relationship with the deceased that does not change can be as troubling for a child as no relationship with the deceased at all.

"I call this 'finding an appropriate place for the deceased," Dr. Worden said.

"An appropriate memorialization enables the child to go on with his life; an inappropriate one keeps him from progressing."

In the study researchers have uncovered both extremes.

A 12-year-old boy who told the interviewer, "My father is here," was an example of an "appropriate" memorialization.

Asked by the interviewer what he meant, the boy replied, "Whenever I take a test, I can feel my father sitting next to me and encouraging me to do well."

Yet another child — a junior high school-aged girl — told the interviewer, "My mother would kill me if she saw my grades. Grades were very important to her. I can just see her up there yelling at me."

"But it wasn't a terror kind of thing," Dr. Silverman said. "It was kind of humorous. The little girl told her father about it too. She said it made them both feel good that they could remember her mother like that, and she promised her father that she would improve her grades."

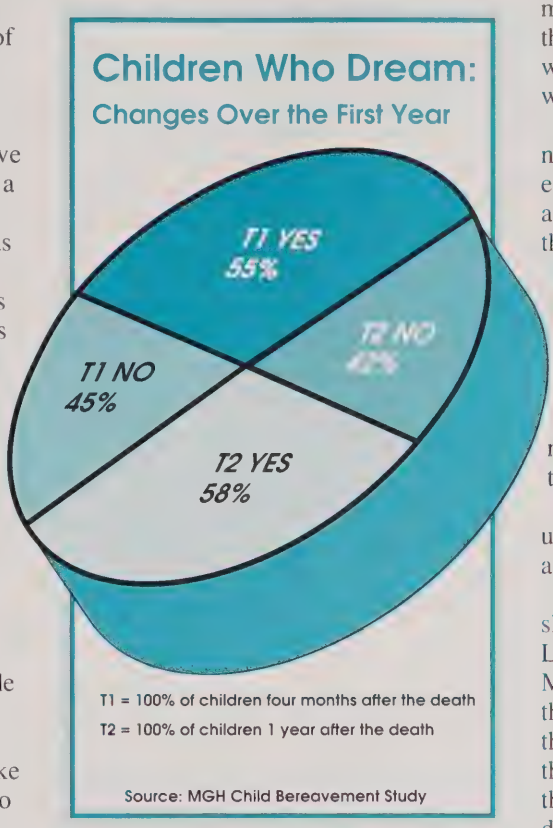
Examples of "inappropriate" connections were illustrated by children afraid to do something — play sports, ride a motorcycle, etc. — because the dead parent would not approve.

Tokens and dreams of the deceased also appear to be critical links in helping the child build a connection to the deceased.

"The objects the child keeps don't have any magical quality for the kids," Dr. Silverman said. "They don't think of them as magic. They're just a connection; something to remember the deceased."

In healthy, well-adjusted children, preliminary results from the study indicate that the child's relationship to the object will change over time. "Objects seem to take on less meaning and less intensity for the child over time," Dr. Worden said. One 15-year-old boy in the study had taken his father's Navy cap right after the death. At first the boy kept the hat hung on his bedpost. By the second anniversary of his father's death, the boy had moved the hat to a corner of his closet.

Such a lessening of intensity around the keepsake appears normal, said the researchers, although they are continuing to study this phenomenon over time.




Dreaming about the deceased — both dead and alive — was common among most of the children. "We don't know if it matters that the parent is alive or dead in the dream," Dr. Worden said. "On the whole, dreaming seems to be a comforting way for children to experience the parent."

Dr. Worden said the surviving parent needs to not only help the child experience the grief and pain from the loss, but also to aid in the child's construction of the deceased.

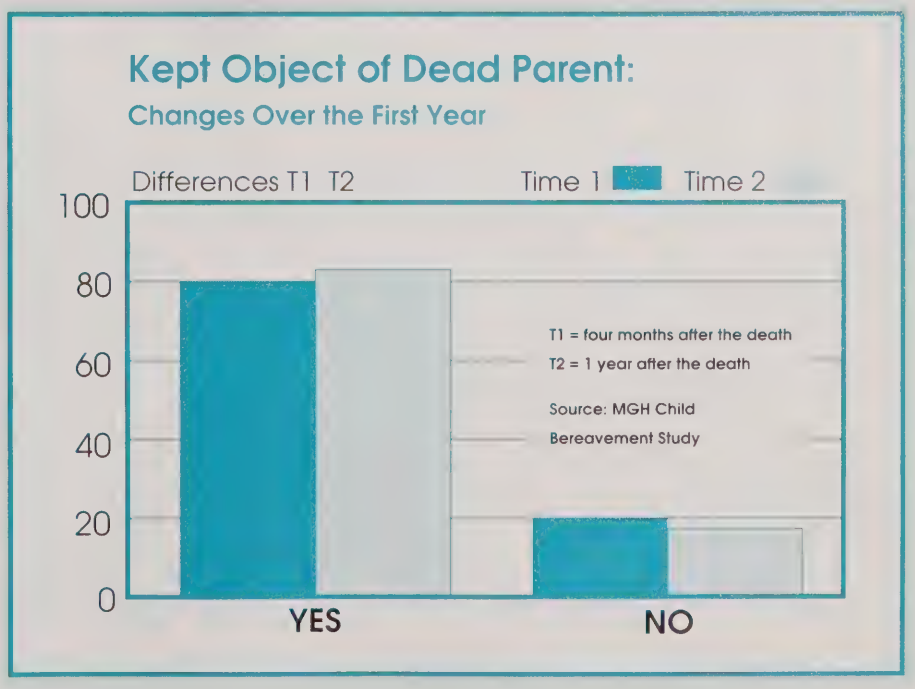
"It's up to the surviving parent to foster discussion about the deceased," Dr. Worden said. "If it's left up to the child, he is sometimes afraid he is going to make the parent more sad by talking about the dead parent. So I think it's really up to the surviving parent to take the lead."

The child's environment also contributes to his overall well-being and how he adjusts to a parental death.

"This is not a simple causal relationship," said Dr. Silverman, who is also a Lecturer on Social Welfare at Harvard Medical School. "You have to look at these children in their whole context — their developmental age, their position in the family, the nature of the death, how the surviving parent copes. Men cope differently than women. It is not simply a death and then an outcome for these kids. They are going to be changed forever."

Dr. Worden said the change for bereaved children goes far beyond simply the death of a parent.

"What you are really dealing with is the death of a lifestyle." ■



# — Noted Researcher Coming Home

*(Continued from Page 1)*
includes Dr. Sachs' appointment as the first Paul S. Russell / Warner Lambert Professor of Surgery at Harvard Medical School. It was Dr. Russell, the founder of the MGH Transplantation Unit, who first introduced a second-year medical student with an interest in research to the field of transplantation.

"I consider Paul one of my most important mentors," Dr. Sachs said recently. "He's had an enormously important influence on me. I'm extremely proud and honored to be the first to hold the chair that will bear his name. He represents the best of both basic science and patient care in this field."

**"I feel very strongly that the future of transplantation and specific tolerance is going to involve both bone marrow transplantation and organ transplantation. By that I mean the bone marrow will be the vehicle by which we induce tolerance, which then permits transplantation of any organ."**

**— Dr. David H. Sachs**

In fact Dr. Sachs said the opportunity to interact with both laboratory investigators and practicing physicians interested in transplantation is what led him to leave the NIH and return to the MGH.

"My hope is to be able to apply the research findings that we've made in animal models to clinical protocols," Dr. Sachs said. "I want to be in an area where I can again collaborate closely with clinical transplanters who are excellent. And the MGH is the best place in the world that I can think of to do that."

Over the past 20 years Dr. Sachs, the Chief of the Immunology Branch of the National Cancer Institute, has achieved international recognition for his work in basic science and preclinical studies. *He has devoted his career to transplantation research. As the author of more than 300 scientific papers, he is considered a leading authority in this field.* In all of his research, his goal remains unchanged from that first formulated in Dr. Russell's laboratory more than 20 years ago — specific transplantation tolerance.

Among Dr. Sachs' many scientific achievements in the field of transplantation was his discovery in 1973 of Class II antigens on B lymphocytes, an important class of immunologically active cells. Antigens are substances recognized as "foreign" by the body's immune system and which trigger an immune reaction.

One major system of antigens is encoded by genes (units of inheritance) of what is called the major histocompatibility complex (MHC). The MHC is present in all mammals. It is the major determinant of what will happen to a transplant. Two individuals are said to be histocompatible (literally "tissue compatible") if they share a sufficient number of antigens so that a transplant is accepted.

Scientists knew the genes of the MHC encoded a group of antigens that are found on all cells and which were known to cause rejection.

But scientists did not know there was another group of antigens within the MHC found only on certain cells of the immune system. This second group, first reported by Dr. Sachs and his colleagues in 1973, is now called Class II antigens. The Class II antigens have since been found in the MHC of all mammalian species. Subsequent research is showing them to be the most important antigens in determining transplant survival.

"I think the understanding of the kinds of antigens determined by the MHC has had very important consequences for typing for transplantation and will continue to do so," Dr. Sachs said.

Another major achievement to come out of Dr. Sachs' laboratory is the production of monoclonal (single cell) antibodies against Class I and Class II antigens of the MHC. Dr. Sachs has produced antibodies primarily against the mouse MHC but also against the pig and the human MHC.

These antibodies have been used for studies of the chemistry and function of the MHC and are considered standards of reference throughout the world.

"There is a large panel of such antibodies that has been very useful and of great importance in helping us dissect the

structure of the MHC at a basic level," Dr. Sachs said.

Another significant contribution Dr. Sachs has made to transplantation research is his development of a large animal model for prehuman studies.

"I decided back in the early 70s that we needed something besides the mouse as a preclinical model for transplantation," Dr. Sachs said. "Many results one obtains in the mouse cannot be translated directly into clinical protocols. It's often too big a step to go from the mouse to man. We needed an intermediate step."

Dr. Sachs' answer was partially inbred miniature swine. As a large animal model for studies of transplantation biology, the pig proved ideal. Of all the possible large animal species, it was the only one in which scientists could control the MHC genes. "When you come right down to it, the pig is pretty much like a very large mouse in terms of our ability to control the genetics," Dr. Sachs said.

The pig has large litters (between 3 and 10 offspring), reaches sexual maturity in about 4 to 6 months, and has a reproductive cycle every three weeks. "In a relatively short period of time, we were able to develop herds of pigs where the MHC is inbred," Dr. Sachs said.

Besides genetics, the pig has many other advantages as a preclinical model. These pigs are similar to humans in size and also in their physiologic and immunologic characteristics. They are also potential donors for cross species transplants (xenografts).

Dr. Sachs has used the large animal model to make many important discoveries. Among them was his discovery that Class II antigen matching is of much greater importance than Class I antigen matching in determining organ transplant survival.

"That investigation is something we're pursuing very actively right now in relation to clinical transplantation," Dr. Sachs said.

Dr. Sachs points out that his efforts for organ transplantation and research based in the hospital's already well-established Transplantation Unit will need to focus also on the field of bone marrow transplantation.

Currently the MGH does not perform bone marrow transplants, but a bone marrow unit will be established in the near future. The MGH has also applied to the state for external approval.

"I feel very strongly that the future of transplantation and specific tolerance is going to involve both bone marrow transplantation and organ transplantation," Dr. Sachs said. "By that I mean the bone marrow will be the vehicle by which we induce tolerance, which then permits transplantation of any organ."

Researchers already know from animal experiments in mice and from Dr. Sachs' laboratory in pigs that a successful bone marrow transplant will leave an animal specifically tolerant to any other tissue or organ from the original donor. It will be important to adapt these studies to human bone marrow transplants.

"The trouble, however, with that approach is that bone marrow transplantation itself is a very serious procedure," Dr. Sachs said. "We wouldn't use current procedures in order to get a kidney to take. Instead we use drugs like cyclosporine [an anti-rejection drug]. *But if we can make the bone marrow transplant much less toxic and more acceptable clinically — and we think we can — then that would provide a way to induce tolerance. And once you have tolerance you don't need any more drugs.*"

Dr. Sachs and his colleagues are working on several different hypotheses and approaches to bone marrow transplantation, and he is looking forward to continuing that work here.

"I think these two fields — bone marrow transplantation and organ transplantation — really deserve to be together. The research is very similar. And I'm hopeful that because the MGH has the advantage of being able to build up a bone marrow transplant program in a place where there is already an outstanding organ transplantation program, these two programs can work together. I hope that our research laboratory can play a role in that process by collaborating with both."

But Dr. Sachs warns that translating results from the laboratory to the patient is a slow process. It does not happen overnight and sometimes it does not even happen over years.

"All of these things take time. They are best done in a setting where one has the ability to go from the mouse to the pig to the monkey to man. All of this is possible at the MGH." ■

*Dr. David H. Sachs, who trained at the MGH more than 20 years ago, will return to the hospital this spring as the first Director of the Transplantation Biology Research Center.*

# —"Father Figure" Changing Roles

*(Continued from Page 1)*
career that began late one evening in the summer of 1954.

Dr. Russell, then a 28-year-old MGH surgical resident just back from military service during the Korean War, was spending the few minutes between shifts boning up on his reading in the hospital's medical library.

That night, while poring over old medical journals, he chanced upon the now-famous paper in *Nature* by Professor Peter Medawar. In the paper Dr. Medawar and his British colleagues reported their discovery of "actively acquired tolerance" of skin grafts in mice. By injecting adult mice with foreign cells early in life, Dr. Medawar found the mice would accept skin grafts from the original cell donor.

"I thought that looked pretty impressive," Dr. Russell said. "But at that time not too many other people in medicine were very interested in this work. It's hard to think back to what it was like then, but the idea of transplanting an organ was a very far out kind of notion and was almost considered bizarre by some people.

"So I wasn't at all sure this line of investigation was ever going to become useful clinically. But I was very interested in it as a scientific subject, and obviously it was something that *might* eventually become practical. So I thought it might be fun. I was also terribly intrigued by the department where this work was being done, and of course by Peter Medawar."

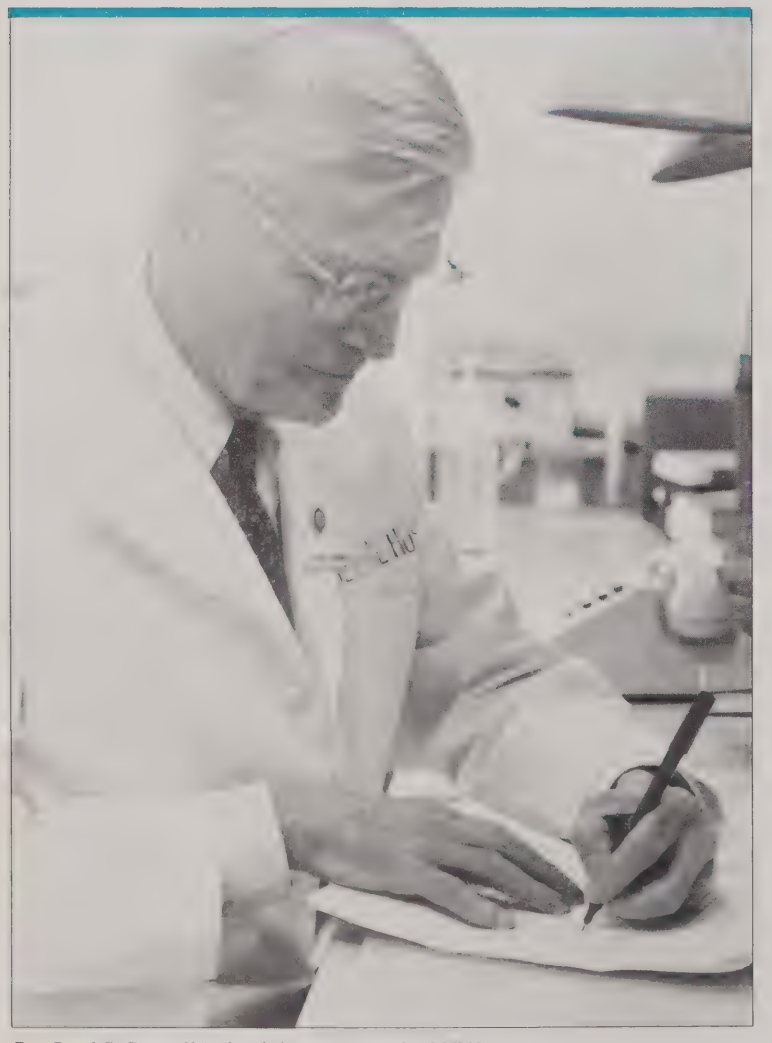
The great Dr. Medawar, however, who later won the 1960 Nobel Prize in physiology or medicine and was knighted for his work on immunological tolerance, was not so sure he should welcome the intrusion of this young foreign surgeon. His reply to Dr. Russell's offer to come to London to work in Dr. Medawar's laboratory was "a cheerful and kindly turn down."

Undaunted Dr. Russell wrote again and this time Dr. Medawar relented. In September 1954, Dr. Russell left the MGH for a year to become the first foreign visitor and one of only two "medically qualified" members of Professor Medawar's Department of Zoology at University College in London.

His London experience made a lasting impression on Dr. Russell. Later, when he founded the MGH Transplantation Unit in 1963, the respect he had gained in Dr. Medawar's laboratory for basic scientific research was to become an underlying theme of the new department.

"A central part of Paul's thinking is that research and clinical work in transplantation should go hand in hand," said Dr. Hugh Auchincloss, Chief of Pancreatic Transplantation. "He was a real visionary in that respect."

The physician/researcher that Dr. Russell embodied so well in his own career and fostered within the Transplantation Unit is a combination that is growing more and more rare in medicine. Across the country, the number of MDs heading research laboratories continues to shrink. Dr. Russell believes this trend is a major problem facing research institutions.



*Dr. Paul S. Russell in his laboratory at the MGH*

**"When young people come into this room and ask me how they can possibly do research and see patients at the same time, I tel them it's impossible. It's absolutely impossible. But at the same time it's essential."**

**— Dr. Paul S. Russell**

"When young people come into this room and ask me how they can possibly do research and see patients at the same time, I tell them it's impossible. It's absolutely impossible. But at the same time it's essential."

Dr. Russell believes the only way practicing physicians can do necessary, important scientific research is through a team approach. Early in the history of the Transplantation Unit he established a group practice for staff members. All the

staff members participate in the practice and contribute their fees. Each then draws a salary, which is based not only on the monetary contributions to the practice but also on all the intellectual and innovative contributions, whether it be patient care or laboratory oriented.

Formation of the group also enhanced patient care. For instance, the MGH transplant group was one of the first in the country to include a psychiatrist — a service not reimbursed by some health insurance companies since a psychiatrist is not the primary or even secondary physician.

Under Dr. Russell's direction, research has become a major priority of the Transplantation Unit. Over the years, MGH researchers have pioneered many new treatments and contributed greatly to current understanding of immunology.

One of the major discoveries to come out of MGH laboratories was the use of antibodies to lymphocytes, the principal cells causing rejection. MGH researchers developed some of these antibodies in conjunction with the Upjohn Company. Now the antibodies are used worldwide to control transplant rejection.

MGH researchers, in conjunction with Ortho Pharmaceuticals, also developed the drug OKT-3. This powerful agent, a monoclonal antibody, is directed specifically against the cells that cause rejection. OKT-3 was first selected and used at the MGH and is believed to be the first monoclonal antibody ever given to a patient for treatment of any condition. It also is now used worldwide to fight transplant rejection.

While the many scientific achievements have given Dr. Russell much satisfaction over the years, patient care continues to be his primary motivator.

On April 24, 1963, he led the hospital's first kidney transplant operation. Since then he has presided over more than 1,000 kidney transplants as well as the addition of heart, liver, and pancreas organ transplants. MGH surgeons also carry out bone transplants, and last summer performed the hospital's first lung transplant.

"With many of these operations, especially in the liver program, we tend to take on desperately ill patients," said Dr. Russell, who will continue to see patients and do research at the MGH, as well as retain his chair as John Homans Professor of Surgery at Harvard Medical School. "Many of these people are absolutely out of bounds by any previous judgment. But we are able to turn them back into normal people again. It really gives me a lot of joy to see that happen. It's marvelous."

But in some ways that once bizarre notion of transplanting an organ has led to problems.

"The question of whether medical technology has outstripped our ability to pay for it and our ability to give it to everyone is important to us," Dr. Russell said.

The ethics of transplantation — who lives, who dies, and who decides — are very much on Dr. Russell's mind these days. He reads widely and lectures on the subject. "Essentially, I think, what we need to know is how much benefit we get from a certain procedure in comparison to its cost. It's not an easy thing to establish these facts, but I think we can come up with much better quantifiable measures of what the effectiveness of a certain treatment is compared to another course of action."

As for the shortage of donor organs, the scientist in Dr. Russell dismisses this as a mere "technical" problem.

He points to cross-species (xenogeneic) organ transplants as a very near reality and one that MGH researchers, led by Dr. Auchincloss, are working hard on. "In some cases that's physiologically perfectly logical," Dr. Russell said. "Specific tissues like the islets of Langerhans of the pancreas, which make insulin, would be physiologically pretty much the same from one species to another."

In a more futuristic, science fiction vein, Dr. Russell points to the possibility of someday growing organs in a test tube from a few cells. "We're a long way from that right now but there's no theoretical reason why we can't get some cells to grow up into a new organ."

More immediately, he points to the progress being made with artificial organs, particularly with the artificial heart.

"Technically there is no limit to the possibilities open to us," Dr. Russell said. "All of our research is part of the same fabric — to restore functions that are missing from an otherwise useful person. I think that is a dignified and reasonable objective." ■

# *Flatfeet Do Not Have to Be Painful*

DOCTORS have learned many things about flatfeet since the 1940s, when "weak arches" were enough to keep a man out of the Army.

"There was no reason for the military to reject *all* prospective recruits with flatfeet during World War II," said Dr. Robert Scardina, Chief of the MGH Podiatric Unit. "The flatfoot condition alone does not always accurately predict symptoms or the need for subsequent treatment."

In fact, many individuals with flatfeet never experience any significant pain or symptoms. And for those who do complain of foot, leg, or lower back pain because of fallen or weak arches, the remedy is almost always conservative.

Flatfeet — a condition caused by the collapse of the medial arch of the foot — is among the most common of foot maladies in the general population. In the pediatric population, flatfeet and toeing-in are the

*(Concluded on Page 8)*

*Dr. Scardina prepares a neutral position cast from which a pair of custom orthoses will be made.*

## — Flatfeet

*(Concluded from Page 7)*

two most common reasons for a parent to bring a child to a podiatrist.

But Dr. Scardina says many parents who bring their early walkers to a doctor because of flatfeet may be making the same mistake Army recruiters made during World War II.

"The apparent foot misalignment may be insufficient reason alone to seek professional care for flatfeet," Dr. Scardina said.

Almost all children from the time they begin walking until about the age of two or three have observable flatfeet because of an overabundance of fat tissue in the medial arch.

While most children will grow out of early flatfeet, there are two types of congenital flatfeet that do require early treatment. In the first, called a vertical talus (ankle bone), the ankle bone and heel bone (calcaneus) are pitched downward to an excessive degree while the front of the foot pitches up. Treatment usually involves initial gradual stretching of the tendons and ligaments about the foot and ankle as much as possible, and then operating to further correct and stabilize the foot.

In the second type of congenital flatfoot, the foot is overly dorsiflexed (turned up and out) at birth with excessive skin folds along the outside of the ankle. That condition usually responds very well to manipulation and plaster (serial) casting. The correction is then preserved with orthopedic shoes and/or custom foot orthoses (inserts).

Pediatric vs adult is only one way of broadly classifying flatfeet. Podiatrists also categorize flatfeet as congenital vs acquired, rigid vs flexible or symptomatic vs asymptomatic.

Flexible flatfeet are the most common type of flatfeet among both children and adults. In this condition the foot has a normal arch in a non-weightbearing position. As soon as weight is put on the foot, however, the medial (inside) arch is lost — either partially or completely. Rigid flatfeet never have an arch. "The rigid flatfoot is typically more symptomatic and usually indicates a more pathological process," Dr. Scardina said. Fortunately, it is also much less common than the flexible flatfoot.

Flatfeet — whether rigid or flexible — are not always symptomatic, and all do not require treatment. "Simply having flatfeet is not a reason to warrant treatment, conservative or otherwise, especially in the adult population," said Dr. Scardina, who is also an Instructor in Orthopaedic Surgery at Harvard Medical School.

*Dr. Scardina evaluates the structural deformity causing a painful case of flatfeet.*

If the condition is accompanied by pain (either in the foot, leg, or lower back), altered foot mobility (limited or excessive), significant structural deformity in the legs and/or feet, or neuromuscular disease (e.g. cerebral palsy), connective tissue disease (e.g. Ehlers-Danlos syndrome), or inflammatory joint disease (e.g. rheumatoid arthritis), a specialist should be consulted. Most symptomatic flatfeet — whether rigid or flexible — can be successfully managed conservatively. Foot orthoses include a wide range of devices including: custom made and commercially available shoe inserts, shoe modifications and prescription shoes.

Podiatrists are divided over the role and effectiveness of exercises in the treatment of flatfeet. Some doctors favor strengthening of the leg muscles which pull up the arch, while others feel that stretching the tight calf muscles in the heel cord may be even more helpful.

Setting realistic goals is also a necessary part of any conservative treatment regimen for flatfeet, Dr. Scardina said. "Someone with symptomatic flatfeet who aspires to be a marathon runner might be wise to change his athletic goals and choose to take up cycling or swimming."

Occasionally, conservative treatments will be unsuccessful, and a lifestyle change is not possible for a person with severe symptomatic flatfeet. In these instances more radical surgical treatment to correct the condition may be necessary. ■

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# A Simple Solution for Infant Diarrhea

A SIMPLE, over-the-counter solution available in most grocery and drug stores could prevent as many as 10 percent of all unnecessary infant deaths in this country.

Despite this fact, however, many parents and pediatricians continue to wrongly prescribe apple juice and soft drinks for children suffering from diarrhea.

"The only good thing about these fluids is that they contain water," said Dr. Ronald E. Kleinman, Associate Chief of the MGH Children's Service. "But they can actually produce more harm than good."

Although diarrhea is not the overwhelming problem in the United States that it is in developing countries, where it is the leading cause of infant deaths, it is still a major health hazard. Severe diarrheal illness accounts for as many as 20 percent of all infant acute care visits to U.S. hospitals and 1 in 10 preventable deaths.

But a highly effective treatment for diarrhea called Oral Rehydration Therapy (ORT) continues to be largely ignored by parents and doctors.

"We are so high-tech and so used to using intravenous fluids that something as simple as an oral fluid is slow to become accepted," Dr. Kleinman said. "The ORT solutions have in fact been much more widely accepted in the third world than they have here."

ORT is a water, salt, sugar solution optimally formulated to promote the absorption of water from the intestines.

"The solutions are very effective," said Dr. Kleinman, who is also Chief of Pediatric GI and Nutrition at the MGH. "They allow you to keep a youngster at home and avoid the use of IV fluids. They can reduce the cost of treating diarrheal illness by thousands of dollars for a single episode."

Although ORT solutions have been available for more than 20 years, Dr. Kleinman said many pediatricians continue to prescribe fluids such as apple juice, soft drinks, soups, teas, etc., for diarrhea. These fluids either contain too much sugar, which will actually promote diarrhea, or too much or too little salt, which also makes them inappropriate.

The widely prescribed practice of stopping an infant's food intake during severe bouts of diarrhea can also do more harm than good, Dr. Kleinman said.

"If the child starts off malnourished and gets into one of these bouts, the diarrhea tends to linger longer," Dr. Kleinman said. "Not feeding the child only tends to

*(Concluded on Page 6)*

## *How the Brain Recognizes the Objects We See*

NEARLY half the information the brain receives comes to it through our eyes. That fact is a testament, if ever one was needed, of the primacy of vision among the senses.

Two MGH researchers are studying how the brain uses the information it receives from the eyes to recognize objects.

The three-year study, called Neuropsychological Components of

***Related Stories on Pages 4-5***

Object Recognition, utilizes a battery of specially designed visual tests in an

*(Continued on Page 2)*

*Mona Herron of Wakefield, MA, is given a perceptual scanning task to test her object recognition skills.*

## INSIDE

Neuroscience Focuses on Brain Function
*Page 4*

Measles Makes a Comeback
*Page 7*

EDITORIAL

# Serious Gap in Education and Funding

HIGH TECHNOLOGY has made American medicine a magnet for the sick of the world. As physicians know, however, judging when to use more exotic treatments is as important as the skill to use them well. That is because for a particular patient the risk involved may outweigh the need. A simpler remedy or no treatment at all may be the wiser choice.

So it is with a common, potentially fatal, infant malady, diarrhea. Accounting for as many as one in five acute care infant visits to hospitals in the United States, diarrhea carries a toll of up to 1 in every 10 preventable infant deaths. As a page 1 article states, the best treatment frequently involves simple, effective, inexpensive, commercial products. So simple that parents can often treat the child at home themselves *after a telephone conversation with the family pediatrician*. Home treatment would in most instances work very well while saving Americans hundreds of millions of dollars a year in hospital bills.

Third world nations, known for high infant mortality rates, have by contrast been relatively quick to accept the commercial products, and they are not new. Why not the United States? America's penchant for high technology, in this case special intravenously administered fluids, is part of the answer. Not the entire one by any means. When pediatricians prescribe a home treatment for infant diarrhea - as they usually do - they commonly recommend fluids like apple juice which *may* help somewhat but may even *exacerbate* the problem. A major part of the difficulty therefore is physician reliance on old-fashioned remedies that are usually best forgotten. What is demanded by the facts is a concerted educational program to change the treatment routine of physicians and improve the knowledge of parents as well. In this instance the public itself may become an important part of the instrument of change.

There is yet another major concern. Serious infant diarrhea frequently strikes among the poor, the very people who need more than education to resolve the problem. Often they are unable to provide the nutritious diet requisite for the very young. Even four dollars for the commercial preparations may exceed the means of these families. Sufficient Medicaid support - and, in the long run, perhaps training for jobs or better jobs for the poor - may be an answer.

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THE HEADLINE for the same page 1 article appropriately contains the words "Infant Diarrhea." No surprise there. Even though the majority of MGH News readers are lay people, words like diarrhea are a natural part of a medical story - even in a page 1 headline. It was not always so. In 1955, MGH cardiologist Dr. Paul Dudley White startled the news media, not to mention the public, when he reported that President Eisenhower, recuperating from a heart attack, had a "normal bowel movement." In those days such elemental matters were avoided in public.

Dr. White was merely being Dr. White. He enjoyed raising eyebrows to stress a point. And raise eyebrows he did. A member of the British press covering the news conference said to the cardiologist: "Dr. White, you certainly are very frank. Just suppose that our Queen were ill. . ." Dr. White, however, was pleased that he caused a stir because it heightened attention to his message. The point was that the bowel movement was of medical significance to the President's recovery. In describing a patient's progress toward recovery, he believed people should not be embarrassed to mention a relevant natural act. ■

## — *Vision*

*(Continued from Page 1)*

effort to detect and identify defects in the pathways and brain centers concerned with visual processing.

"The hope is that by understanding the aspects of vision that involve accessing stored information - the memory-driven parts of vision, not just the parts driven by sight - we will be better able to diagnose the underlying problem and eventually treat it," said Dr. Shirley H. Wray, Director of the MGH Unit for Neurovisual Disorders and co-investigator of the object recognition study.

The patients referred to the MGH study come with a variety of vague complaints - "I can't see well; I can't read." One 68-year-old woman saw black fences everywhere she looked. A well-known architect with 20/20 vision could not recognize on paper or re-draw from memory three-dimensional objects, such as a staircase, although he had no trouble recognizing the objects in real life.

Each patient is first tested for any primary visual disorder such as glaucoma, cataract, macula degeneration, etc. Once these conditions are ruled out, the investigators begin testing the patient's visual recognition skills. Patients are tested on their ability to recognize and identify colors, simple shapes, pictures of famous people, music symbols, geometric shapes, etc. In each instance investigators rate not only accuracy but also speed.

"The fact that it might take a patient a while to recognize an object is also evidence there might be a defect," said Dr.

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PHOTOGRAPHS: Pages 1, 3, 4, 7, Linda Goodspeed; Pages 5, 6, Courtesy of Dr. Albert; Vision tests Pages 1, 3, Courtesy of Dr. Wray.

Stephen Kosslyn, Associate Psychologist in Neurology at the MGH and principal investigator of the object recognition study.

The woman who saw fences, for instance, needed abnormally long times to perform the simplest tasks. "Any task that involved accessing information in memory, no matter how briefly, took her an extraordinarily long time compared to tasks that did not involve accessing information in memory," Dr. Kosslyn said.

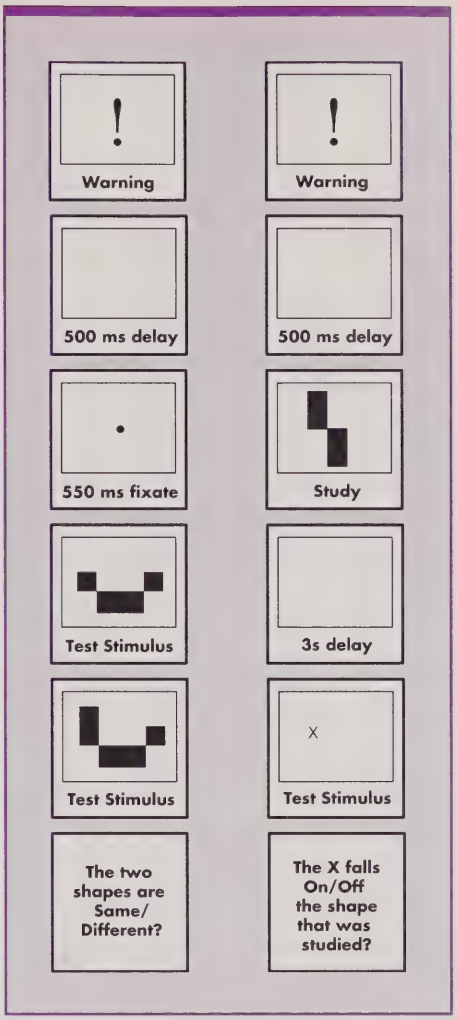
Tests also revealed that the illusory lines went away whenever the woman became absorbed in a task. The lines reappeared as soon as she became bored.

"Unlike most people who get better with practice, she got slower." Dr. Kosslyn said.

The woman's memory and attention problems led the researchers to speculate that some kind of neuroprocessing disorder (at the level of organizing edges and regions into "figures") was creating an illusory fence pattern. And when she became interested in something, she could override the defect.

"This suggests that a stimulant drug, or even coffee, might be effective," Dr. Kosslyn said.

"Before she came to us, everyone had dismissed her as a depressed little old lady," Dr. Wray said. "She, herself, had reached the point where she thought she was going mad."




Researchers now want to try various drug treatments in the hope one will help.

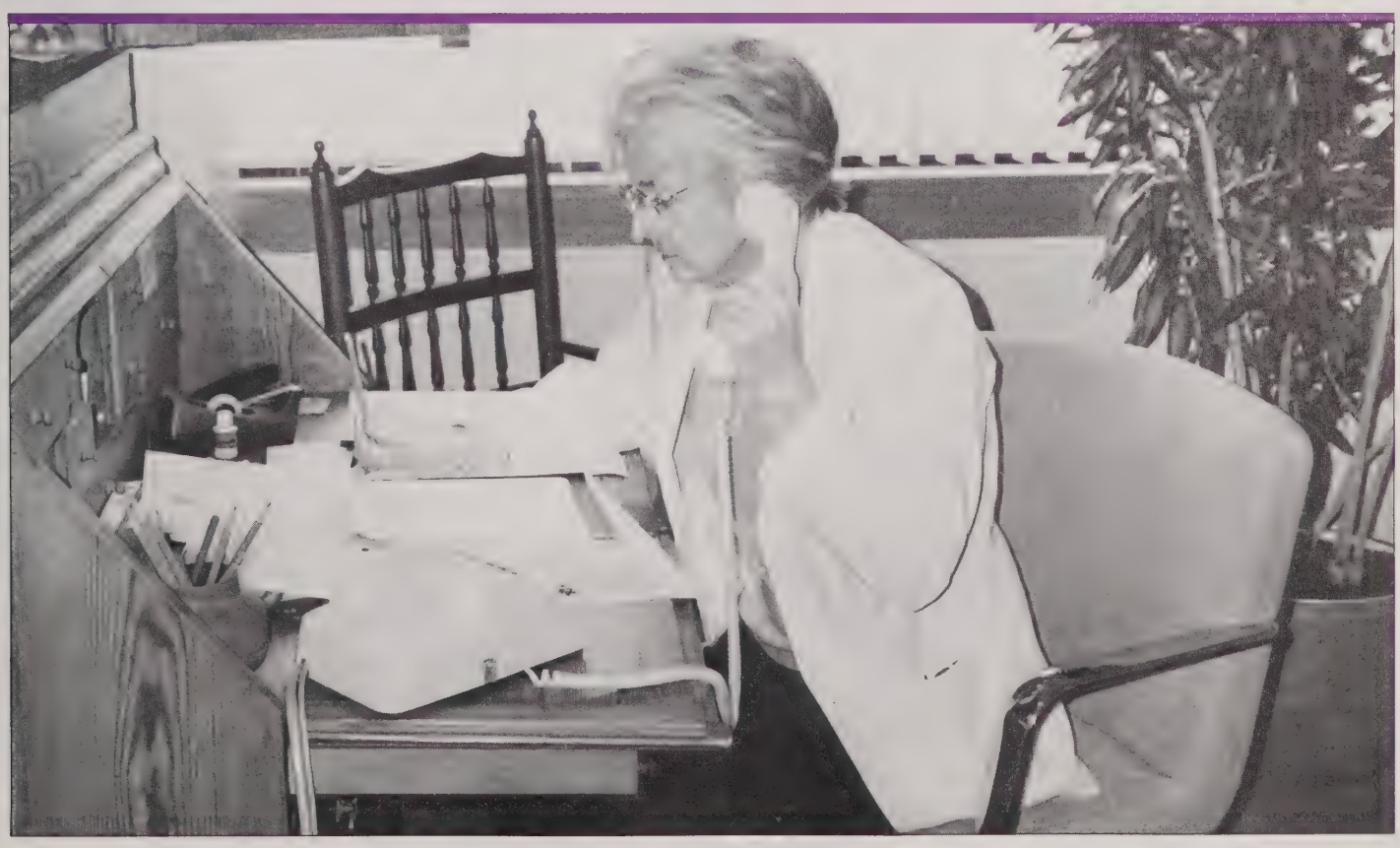
"The value of this type of testing is that the patient is entirely retestable using the same series of variables," said Dr. Wray, who is also Associate Professor of Neurology at Harvard Medical School. "So part of the work is reliable testing to stop patients from being misdiagnosed and/or treated with the wrong drug."

Although the research, which is being funded by the U.S. Air Force, is still at an early stage, investigators hope several such patient applications and testing instruments will eventually flow from it.

The researchers also hope the results will aid them in early diagnosis and treatment of visual processing damage caused by alcohol or drug abuse, stroke, and Alzheimer's disease.

"Out of the several dozen tests we have, it may turn out there's a distinctive profile that characterizes early Alzheimer's for instance," said Dr. Kosslyn, who is also Professor of Psychology at Harvard University. "That's the kind of result we're hoping to find."

As for the Air Force, it hopes to use this type of visual testing to help identify normal people with particular skill at object recognition. This may identify them as particularly ideal candidates to become pilots or navigators. ■



*Dr. Shirley H. Wray, co-investigator of an MGH research study on Neuropsychological Components of Object Recognition.*

# Brain Function Focus of Cognitive Neuroscience Effort

EXCEPT for a mild speech impairment, the young man seemed to have made a complete recovery from the debilitating stroke that struck him down only months before his 40th birthday.

"Everyone who talked to him thought he was of normal or even above normal intelligence," said Dr. David Caplan, an Associate Neurologist in the MGH Neurology Department.

But when doctors tested the young man's verbal intelligence on a standard IQ test, he received the score of a three year old.

"We were dumbfounded," Dr. Caplan said. "Nobody expected him to come out at that level and nobody could figure out why."

The young man's doctors decided to try another approach. Restructuring the verbal test psycholinguistically, the doctors quickly discovered the reason for the man's low test scores.

"It turns out the man could not understand words formed from other words," Dr. Caplan said. "So he could understand 'repeat,' but not 'repetition.' He didn't understand repetition meant repeat as a noun."

Reexamining the standard IQ test, doctors discovered the man's overall score had been dragged down by one subtest. The subtest contained four words all formed from other words. The man missed all four and the word just after the series. Under the rules of the test, five misses in a row was an automatic "F."

"So here's an example of what clearly was a very subtle and particular language processing disturbance that wouldn't necessarily show up in conversation or on a standardized intelligence test," Dr. Caplan said. "But once it's pinpointed it's something that can be worked on by a speech pathologist. This kind of very specific diagnosis and therapy is one of the great hopes and goals of cognitive neuroscience."

Since early in the development of civilization, humans have wondered how the brain actually thinks.

What is the complex series of events and computations that take place between the initial input of sensory data and the actual execution of a movement? How does the brain process the bits and pieces of data that continually bombard it?

In the last 5 to 10 years the combination of high-powered computers that can simulate brain activity on a computer screen and revolutionary radiologic imaging techniques that can actually show this activity in breathtaking detail has made cognitive neuroscience - the study of brain function - one of the most rapidly expanding fields in medicine.

At the MGH the Department of Neurology has recently established a Program in Cognitive Neuroscience. The program brings together experts from the fields of neurology, psychiatry, and radiology at the hospital and beyond.

"The goal is to establish our own research program and then apply that research and the research of others to patient problems," said Dr. Caplan, the Coordinator of the new MGH program.

"As this field gains altitude it's going to touch virtually everything that neurologists do," added Dr. Verne S. Caviness, Chief of Pediatric Neurology, and one of the driving forces behind the neuroscience effort at the MGH. "It is going to modify substantially our entire perspective of how we approach a disease and the criteria we use for diagnosis, evaluation, and rehabilitation."

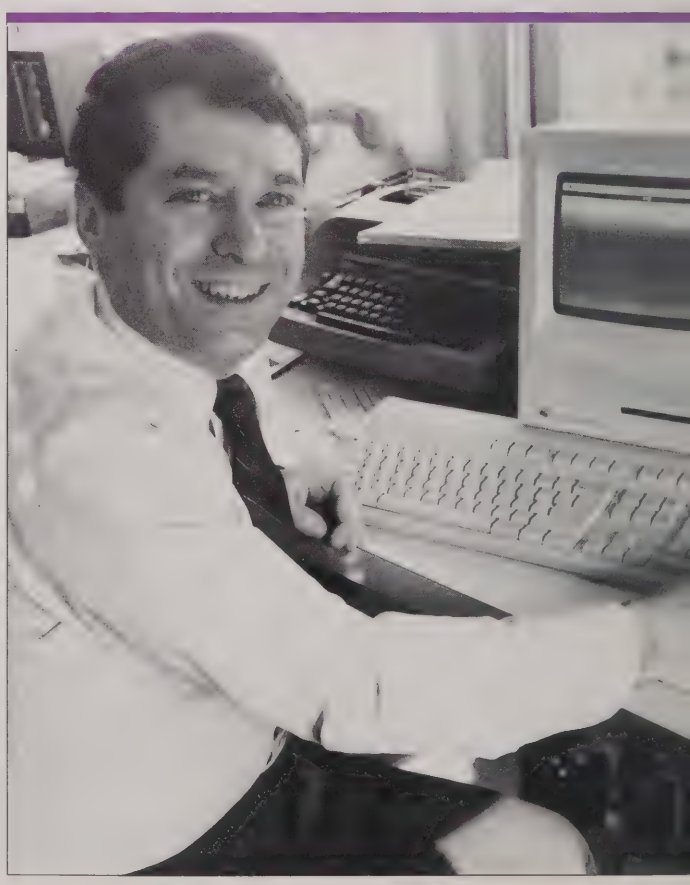
To date much of the work in the field has focused on language and memory because these two aspects of cognition are the easiest to study. But with more and more tools at their disposal, researchers are beginning to zero in on studies of attention, object recognition, conceptualization, and spatial ability. Although highly specific in nature, the research demands an interdisciplinary approach.

"It is typically rare for a person to work alone as a cognitive neuroscientist," said Marilyn Albert, PhD, Co-director of the MGH Geriatric Neurobehavioral Clinic and a career investigator in Alzheimer's research. "More often a problem is conceptualized and people with expertise in many areas are needed to get an answer."

Researchers study brain function in three primary ways - by looking at normal brain activity, at brain damaged activity, and through animal studies.

The introduction of positron emission tomography (PET) scanning (see MGH News, September 1990 *and April 1980) has revolutionized the study of brain activity. PET has provided researcher*s with their first clear look at how the brain uses chemicals. The technology has allowed neurologists to look at where a particular metabolic activity occurs in the brain while a person is carrying out a specific task.

Through the use of PET and other neuroimaging techniques such as CT



*Dr. David Caplan*

(computed tomography) and MRI (magnetic resonance imaging), researchers at Washington University in St. Louis have found there are particular areas of the brain that become active when a person recognizes a visually presented word. And those areas are different from the areas of the brain that become active when a person recognizes a spoken word.

Researchers also use EEGs or a technique called BEAM (brain electrical activity mapping) to measure the distribution of electrical activity across the brain surface. They can use these measurements to determine the amount of brain activity that takes place during a cognitive test. This technique is called "event-related potentials."

"By looking at the distribution of electrical activity in the brain and averaging that over many many trials, we find that the particular part of the signal that's related to a particular cognitive event begins to stand out from the background noise," Dr. Caplan said.

In studies of brain damaged people, researchers use these same neuroimaging techniques to try and match specific lesions in the brain with particular cognitive defects. A person with a certain kind of brain damage, for example, might complain of periodically not being able to recognize objects. That complaint is so vague it is of little use to neurologists trying to diagnose the illness or to therapists trying to treat the cognitive disorder.

But if specific testing of the patient's visual processes can narrow that complaint down to an inability to recognize objects in unusual rotations - a pen that is sideways, for instance, as opposed to straight on - then therapists would have specific information they could use to try to correct the problem.

Furthermore neurologists can use computerized radiologic images of the brain to pinpoint the brain damage. Once they know the location of the cognitive disturbance, they can match it with a disease known to be primarily located in that region - a stroke, for instance, or perhaps a brain tumor, or Alzheimer's disease.

In addition to studying the effects of brain damage and normal brain activity in humans, researchers also study cognitive functions in animals.

"Animal studies have given us an enormous amount of information," Dr. Caplan said. "We can then use that information to generate hypotheses about how human systems work."

From animal studies in monkeys, for instance, researchers have learned much about how the brain processes visual information. It now seems clear from these studies that although information goes from the retina to the occipital lobe in the back of the head, the information is not processed there alone.

Instead the occipital lobe channels the information down one of two major pathways.

Information sent and processed in the temporal lobe is used to recognize an object. Information processed in the parietal lobe is used to locate that object in space.

"This is the kind of information that's come out of visual processing in animal studies," Dr. Caplan said. "Now we can begin to test those insights in humans."

The explosion in cognitive neuroscience would not be possible without computers.

Researchers use computers to simulate cognitive processes and test hypotheses. Computers are also used to test patients and to analyze data.

"We're not simply trying to give an IQ test and make a prediction of how a person is going to perform," Dr. Caviness said. "We're trying to understand how the brain processes information." ■

# *The Difference Between Normal Aging and Alzheimer's Disease*

ALTHOUGH physicians often diagnose Alzheimer's disease during the life of a patient, they cannot be 100 percent sure of the diagnosis until after an autopsy after death.

But if doctors are to have any hope of intervening and perhaps one day reversing this mind-crippling disorder, they must diagnose - and confirm - it early before it begins to destroy a pa-tient's mental capacities beyond repair.

"It is often very difficult to differentiate Alzheimer's disease, when it is mild, from other diseases such as depression or small strokes, or even to distinguish it from cognitive declines due to normal aging," said Marilyn Albert, PhD, Co-director of the MGH Geriatric Neurobehavioral Clinic. "But if we are to have any chance to treat it we have to be able to identify it early when it's mild."

A long-term study headed by Dr. Albert is comparing the effects of normal aging and Alzheimer's disease in hope of discovering where in the brain and how Alzheimer's disease first begins.

The study, which began in 1980 and is being funded by the National Institutes of Health's Institute on Aging, is following 200 healthy people and more than 100 people with Alzheimer's disease.

Using computerized nervous system imaging techniques such as CT (computed tomography), MRI (magnetic resonance imaging), and SPECT (single photon emission computed tomography), Dr. Albert and her colleagues from several other area hospitals can relate changes in behavior and mental ability to physiologic and structural changes in the brain.

During normal aging, researchers have found changes take place in the brain in the absence of any disease. In neuropsychological testing of the participants, they also note declines in cognitive ability.

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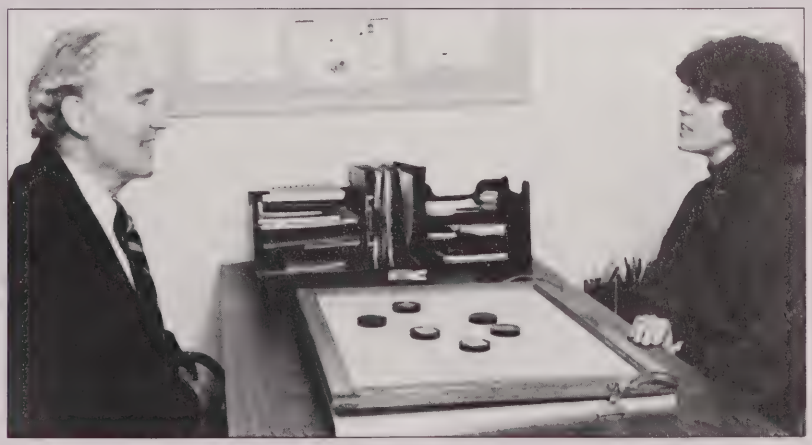


*Dr. Marilyn Albert (right) administers a delayed recognition test.*

## — *Alzheimer's*

*(Concluded from Page 5)*

Mild Alzheimer's disease is distinguished from normal aging when declines occur in two or more mental areas and are severe enough to affect a person's lifestyle.

"We know from testing that as people get older they have more difficulty remembering a lot of information immediately and that they don't retain new information quite as well over a period of time," Dr. Albert said. "Patients with Alzheimer's remember less immediately, but the really dramatic decline is what they lose over a delay, and I'm talking about a very short delay - two or three minutes."

Such differences in cognitive ability between normally aging adults and mild Alzheimer's patients show up in neuropsychological testing. But this testing takes time to administer and skill to interpret. And even then there is room for some doubt.

Researchers hope computer images of the brain will help them to confirm an early diagnosis of Alzheimer's disease quicker, easier, and definitively.

Because of the behavior and particular kind of memory impairment that typifies Alzheimer's patients, researchers are zeroing in on the hippocampal region in the lower back of the brain as the likely site of the origin of the disease.

"So far the techniques that have been the best at showing early changes in the hippocampus are images of brain structure," Dr. Albert said.

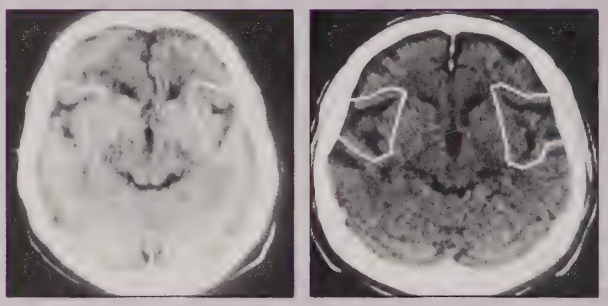
Published results by Dr. Albert and her colleagues show CT has an accuracy rate of about 94 percent in differentiating early Alzheimer's disease from normals. The next step is to examine differences between patients with Alzheimer's disease and other diseases that cause mental declines.

"The long range hope is that we can use neuroimaging to confirm a diagnosis very, very early so that we can intervene and treat people," Dr. Albert said.

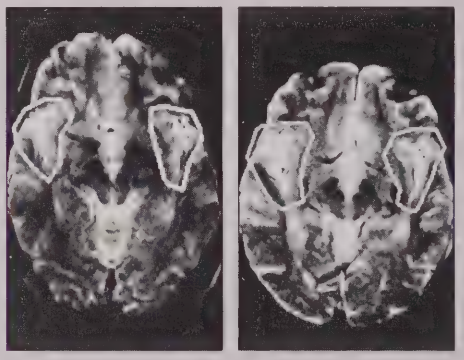
Currently there is no good treatment for Alzheimer's disease. The only therapies are experimental drugs available through drug trials. Protocols for such trials demand early and accurate diagnosis.

"You can imagine if some of the patients in a drug study didn't really have the disease you were trying to cure," Dr. Albert said. "It would be hard to figure out if you had an effective treatment."

But with the advent of earlier, accurate diagnostic techniques, researchers can concentrate on finding a cure for this dreaded disease. ■



*A CT of a normal control (left) is compared to a CT of a mildly impaired Alzheimer's patient with the region around the sylvian fissure outlined. Researchers hope to use neuroimaging techniques such as CT and MRI to confirm an early diagnosis of Alzheimer's disease.*



*An MRI of a normal control (left) and a mildly impaired Alzheimer's patient with the region around the sylvian fissure outlined. The Alzheimer's patient shows evidence of more degeneration in the region.*

## — *Infant Diarrhea*

*(Concluded from Page 1)*

enhance that cycle of malnutrition and make it even more difficult the next time the youngster gets diarrhea.

"Once the child gets back to a normal state of hydration, even if diarrhea is going on, he should be started back on solid food."

Dehydration is the most serious consequence of diarrhea. Signs of dehydration in an infant are decreased urine output, crying without tears, dry mouth, sunken eyes, doughy or loose-feeling skin, and listlessness or excessive sleepiness. Often a pediatrician can prescribe an ORT solution over the telephone from a description of the child's symptoms. If the youngster appears unusually listless, however, or is passing blood in his stools, has a fever, or other serious signs, he should probably be seen by a nurse or physician.

ORT solutions are available under four different brand names: Rehydralyte, Pedialyte, Ricelyte, and Resol. The water, salt, sugar composition of each is similar. Average cost of the solutions is $3.50 to $4 a liter (a little more than a quart). The amount of solution needed to rehydrate a child varies with age. Infants usually need about a liter given over a period of 4 to 24 hours. In 18 states, Medicaid will pay the cost of the solutions. (Massachusetts is not one of them.)

Dr. Kleinman, who is also an Associate Professor of Pediatrics at Harvard Medical School, says both parents and pediatricians need to be educated about Oral Rehydration Therapy.

The International Child Health Foundation is sponsoring the National ORT Project, of which Dr. Kleinman is a member of the managing board. This project has undertaken an educational program to inform both physicians and the public of the need to use these solutions. Dr. Kleinman is also Chairman of the Nutrition Committee of the American Academy of Pediatrics which strongly supports the educational program.

"ORT should be the standard of care for diarrhea. But there are still pediatricians and family physicians who are prescribing those other remedies and inappropriately so in many cases. We need to do a lot of educating around this issue." ■

# *Measles:*

# A Serious Disease Makes A Comeback

MEASLES, on the verge of extinction only a few short years ago, is making a comeback.

Usually associated with childhood, this highly contagious disease is back mainly among young adults who were never vaccinated or inadequately vaccinated.

"People shouldn't make the assumption that just because they had baby shots, they're covered against measles," said Dr. Cyrus C. Hopkins, MGH Epidemiologist and Clinical Director of the Infectious Disease Unit. "People need to sit down and try to document the type of vaccine they had in order to fill in the blanks."

The blanks in measles immunization are increasing among all segments of the population for a number of reasons. Budget cutbacks have eliminated some infant vaccination programs in poor and minority neighborhoods. Large immigrant populations have entered the country without being adequately vaccinated. Some religious communities shun vaccinations for religious reasons. And many adults who have been vaccinated may have received the wrong shots at the wrong age and are now only partially protected against the disease.

"The largest number of measles cases we see today are people who have been only partially immunized, or ineffectively immunized, or their immunization status is waning a bit," Dr. Hopkins said.

The sudden rise in measles cases the last two years is a disappointing turn for physicians - many of whom have grown up having never seen the disease before - and for public health officials who thought they had all but eliminated this serious illness.

Before a vaccine for measles was developed in 1963, the Federal Centers for Disease Control in Atlanta estimated as many as 750,000 Americans came down with the disease every year. One in 10,000 who did, died or suffered serious central nervous system damage.

By the early 1970s, after the introduction of a vaccine, the number of reported measles cases had plummeted to 50,000 a year. And in 1983, a record low of 1,497 cases was reported in the United States.

Since then the number of reported cases has begun to move back upward. More than 18,000 cases were reported in 1989, and 26,000 last year.

This sudden upsurge has continued into 1991. In Philadelphia an outbreak of measles in February struck more than 500 people, killing several. In all of 1990 there were 266 confirmed cases in the city.

People who live and work in close quarters, such as health care workers, prisoners, and college students, have been particularly vulnerable to the disease in recent years.

An outbreak of measles at Boston University in 1985 struck 105 students, forced the rescheduling of dozens of athletic and social events, and prompted the Massachusetts Legislature to pass a law requiring all incoming college students be vaccinated against measles, mumps, and rubella. Most states have similar laws.

Health care institutions have likewise adopted strict documentation and immunization procedures for employees. At the MGH, new hires must prove that they have either had the disease or been vaccinated against it. "If there is any question, employees are strongly encouraged, if it is medically indicated, to get the vaccine," Dr. Hopkins said.

Measles (rubeola) usually begins with the sniffles or a nasal discharge, followed by an early fever and inflammation of the eyes (conjunctivitis). Within a day or two these symptoms, often accompanied now by a cough, deepen, and a prominent, blotchy, red rash appears on the patient's face and torso. Fevers can run very high and continue for several days. "It can be a very serious disease," Dr. Hopkins said, "particularly when it is acquired by an adult." Rubeola differs from rubella (German measles) in severity, length, and consequences. "You don't have the inflammation of the eyes or the nose or the respiratory component with German measles," Dr. Hopkins said. "It usually shows up as a very mild, barely visible rash, sometimes with a few slightly swollen lymph nodes and a low-grade fever. After a few hours or

*(Concluded on Page 8)*

*MGH employee Hau Tran is vaccinated for measles, mumps, and rubella by Linda Thomas, RN, at the MGH Employee Health Office. Most hospitals now require employees either prove they have been vaccinated against measles or receive a new vaccination.*

## — *Measles*

*(Concluded from Page 7)*

a couple of days, at most, it goes away. We suspect most people with German measles do not even see a physician. And even if they do, those symptoms could easily be passed off as a nonspecific, viral illness."

Although it starts mildly, rubella or German measles can cause devastating birth defects when it infects a pregnant woman. A vaccine against the disease was introduced in 1969.

"In many cases we were much more aggressive about German measles because of the possibility of congenital rubella syndrome," Dr. Hopkins said. "Even though we aren't sure rubella is being reported as faithfully, I think, overall, it's been a more effective program."

Three years ago the CDC reported a record low of 225 cases of rubella in the United States. But 396 cases were reported in 1989, and 1,093 last year.

A vaccine against rubeola (regular non-German measles) was introduced in 1963. Initially there were two types of rubeola vaccines, both of which doctors now know had flaws.

"Anybody who received a vaccine between 1963 and '67 or '68 probably did not receive an adequate vaccine," Dr. Hopkins said.

In 1968 the live, attenuated (less virulent) vaccine still in use today came on the market. But as the 1970s progressed, doctors learned they could improve the effectiveness of the vaccine by delaying its injection.

"At first we used to immunize infants at nine months," Dr. Hopkins said. "We later advanced that to 12 months. Now we feel for the vaccine to be the most effective, infants have to be immunized at 15 months."

Doctors also now recommend that children receive a second injection when they reach school-age.

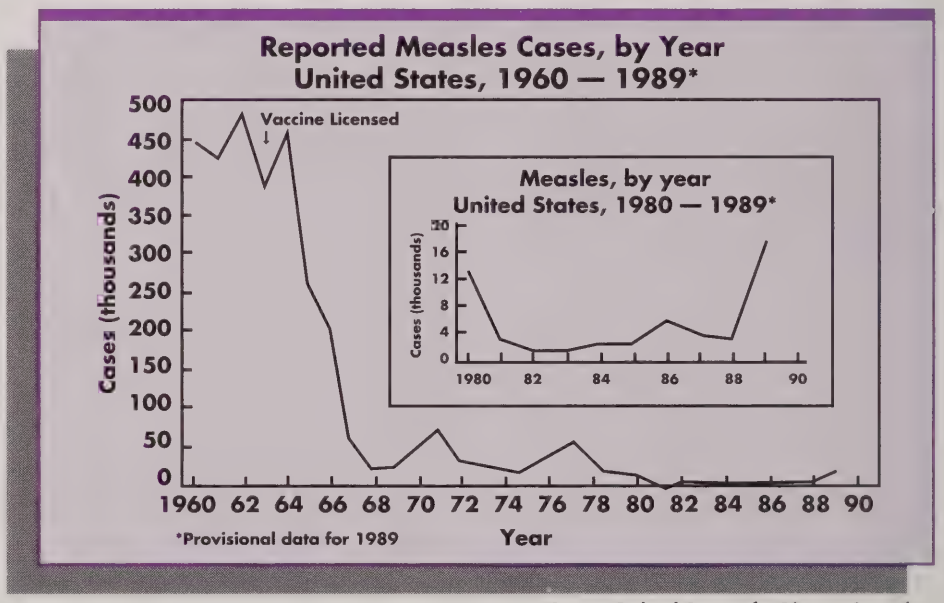
"We're not really sure that you don't need a 'booster' shot with any vaccine," Dr. Hopkins said. "Even if you give what seems to be the perfect vaccine, it may be only 95 percent effective. The person may have a viral illness, the injection might not have been adequate, or properly preserved. There are any number of technical reasons why a vaccine might not take the first time. So it may be only that second dose that makes up those gaps."

Because measles can be spread through the air, doctors believe any vaccine against it must reach at least 98 or 99 percent of the population to contain it.

"There's a concept in vaccine administration that was derived from veterinary medicine called 'herd immunity,'" said Dr. Hopkins, who is also an Associate Professor of Medicine at Harvard Medical School. "Even if you were only able to immunize 90 percent of a herd, an epidemic would not occur because if one cow got sick most of the others around it would be protected.

"But it turns out that herd immunity isn't applicable to measles at all. Because the disease is so contagious, herd immunity doesn't protect the unimmunized. You have to get everybody, or close to it, immunized to prevent an epidemic.

"With the current financial constraints we're facing, I don't know that we'll ever achieve our original goal of eradicating measles. But I think we can certainly come a lot closer than we have so far." ■




Source: Federal Centers for Disease Control

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MGH News

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# Noted Cancer Researcher to Direct New MGH Laboratory

EDWARD E. HARLOW, JR., PhD, the newly appointed Director of the MGH Laboratory of Molecular Oncology, compares cancer research to an elaborate play.

Seemingly unrelated characters move on and off stage; the plot twists and turns, bends back on itself, and lurches forward again. Each act adds another layer of intrigue and mystery.

But then suddenly, unexpectedly, a revelation — so simple, in retrospect, it seems almost inevitable — unites the play's many characters and plot twists into a cohesive whole.

A scene very much like that happened three years ago in Dr. Harlow's cancer laboratory at Cold Spring Harbor, NY.

Dr. Harlow, then a Senior Scientist at the well-known cancer research facility, discovered that two seemingly unrelated cancer-causing genes actually team up to turn a normal cell into a cancer cell. The revelation has greatly simplified the explanation of how certain cancers develop and helped define the direction of cancer research for the next several years.

In February Dr. Harlow brought that new direction to the MGH Cancer Center. The 39-year-old scientist, considered one of the world's leading authorities in the field of oncogenesis (the study of how tumors are formed), will develop and head the hospital's new molecular oncology facility in *(Continued on Page 6)*

*Dr. Edward E. Harlow*

## INSIDE

Spaulding Rehabilitation Hospital *Page 4*

Recruiting Minorities *Page 7*

## *Hospital Forms Reproductive Endocrine Science Center*

SINCE the introduction almost three decades ago of the pill and intrauterine device, no new contraceptive method has been introduced in the United States. And although both the pill and the IUD have been modified over the years to increase their safety and effectiveness, they are still not suitable for use by all couples in all circumstances.

What's worse, there are few alternatives on the horizon.

"There is a crisis developing in contraceptive research in this country," said Dr. William F. Crowley, Jr., Chief of the MGH Reproductive Endocrine Unit. "Because of issues of liability, lack of funding, and other reasons, there is virtually no contraceptive research going on right now in this country."

The problem is so acute, the National Research Council on Contraceptive Development convened a special task force to study the situation and recommend a solution. The committee's report, which appeared last year in the *New England Journal of Medicine*, called on the U.S. medical research community to solve the crisis.

The MGH was listening.

Thanks to a $3.8 million "center" grant from the National Institutes of Health, the hospital's already extensive *(Continued on Page 2)*

EDITORIAL

# Recruiting Minority Physicians

RECRUITING underrepresented minorities to medicine is crucial. It is also clear that recruiting physicians — regardless of color of skin — to the inner city is vital. Finally, to attract large numbers of underrepresented minorities to medicine, there needs to be people of color in visible places in the education process itself.

These truths present a quandary. In recent years the United States had encouraged the production of more generalists and fewer specialists. The government had provided incentives for training family doctors and other nonspecialists. Its hope had been for more generalists and minority generalists who would go into the inner city to practice. In 1982 funding sources for this effort dried up, and this may help explain why years later the inner city, as well as rural America, remains grossly underserved.

Teaching hospitals geographically removed from the inner cities have had difficulty attracting bright young minority physicians to train and even more difficulty in getting them to remain as staff members after training. Part of the reason is that minority groups often feel uncomfortable in cities where they are a distinct, and not always appreciated, minority. Since the staffs of the noninner city hospitals tend to have few underrepresented minority members to serve as role models, African American and Hispanic interns and residents are even less likely to remain after they complete training. For the past several years the MGH has had a special relationship with a Boston public middle school to inspire underprivileged students.

— — —

A PAGE 7 ARTICLE describes a different, more wide-ranging program. Underrepresented minority students in high schools to medical schools are being sought by the MGH to experience the opportunities available to them here by working alongside expert mentors. The students are seeing a side of medicine many never before even thought about.

With the guidance of physician-teachers and scientists, these young students are learning about careers in academic medicine. Some, it is expected, will want to become physicians who treat patients with complex medical problems, teach the next generation of doctors, or develop the diagnoses, treatments, or cures of tomorrow. Some will want to have two or all three of those academic careers. Still others will choose to become generalists at the MGH or similar hospitals or in the inner cities.

Make no mistake about it, substantive progress will take years of labor by people dedicated to achieving these goals. Nevertheless once young minority students begin seeing African Americans and Hispanics becoming world-renowned doctors in leading teaching hospitals, it should no longer be difficult to inspire underrepresented minorities to enter teaching hospitals to train and remain. And to train others who will practice in the inner cities. ■

## —*Reproductive Endocrine Center*

*(Continued from Page 1)*

reproductive research efforts may soon expand into contraception.

"Contraceptive research is one of the areas we've been eager to get into but haven't been able to in the past for various reasons," said Dr. Crowley, Director of the new MGH Reproductive Endocrine Science Center established with the NIH funding. "It's an area where we think we can make a difference."

The new Reproductive Endocrine Science Center brings together several dozen investigators from the Departments of Medicine, Surgery, and Pediatrics under one umbrella. Existing laboratories within these departments are grouped into five "core" facilities, each headed by a core director.

The cores allow individual researchers to interact with colleagues in different scientific specialties in a way not previously possible.

"All of the various laboratories in the center have enormous expertise in single areas, but they may not have the broad expertise that the entire center offers," said Dr. Patricia K. Donahoe, Associate Director of the new center and Chief of Pediatric Surgery. "Putting in place these cores is going to allow every single laboratory and every single investigator in reproductive biology to have access to equipment and expertise ranging from the gene all the way to the patient. It broadens everyone's base."

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Dr. Donahoe's own research on mullerian inhibiting substance is a vivid example of the scope and possibilities created by the new center format.

Mullerian inhibiting substance (MIS) is made by both the fetal testes and the adult ovary. In the female, the absence of MIS allows the mullerian ducts to evolve into the fallopian tubes, uterus, and upper one-third of the vagina. In the male, MIS causes those structures not to develop.

Several disorders can result from defects in the mullerian inhibiting substance, including intersex anomalies (individuals who have characteristics of each sex). Several ovarian tumors have also been found to produce MIS, making the substance a useful marker for following recurrent tumors in these women.

Dr. Donahoe, who with scientists at Biogen, a biotechnology firm in Cambridge, MA, and Switzerland, cloned the gene that produces MIS in 1987, is now pursuing several diagnostic and treatment applications for these disorders.

Down the road, MIS could also have value as a possible contraceptive agent. "The idea would be that we could give MIS to regulate oocyte (the female egg) development and ovulation," said Dr. Michael L. Gustafson, a research fellow in the Pediatric Surgery Research Laboratory.

Creation of the new center will help Dr. Donahoe and her colleagues explore all the possible applications of the mullerian inhibiting substance.

"Membership in the center gives me access to expertise I wouldn't normally have," said Dr. Donahoe, who has just ended a three-year term as Chairperson of the hospital's Executive Committee on Research. "It's a tremendous opportunity."

The new center will also allow Dr. Crowley's Reproductive Endocrinology Unit to expand its research on how the brain controls reproduction and possibly also apply that knowledge to contraception.

Among the hormones Dr. Crowley has been studying are the gonadotropins.

Gonadotropins are pituitary hormones that stimulate the ovary and testes to develop at puberty and function in adulthood. "The pituitary hormone FSH (follicle-stimulating hormone) is a hormone you need for only one purpose in the male and that's reproduction," Dr. Crowley said. "So if we could block that hormone which has no other known biologic function and achieve an isolated control of reproductive processes and provide contraception in the male that would be a considerable achievement."

Dr. Crowley's investigation of the gonadotropin-releasing hormone (GnRH) has already yielded several important treatments for female infertility and precocious puberty (*MGH News, September 1985*).

"We discovered that if you delivered natural sequenced GnRH in a pulsatile (pulsing) fashion, much like a strobe light, you could stimulate the pituitary of women who had no menstrual period to reproduce a menstrual period, to ovulate, and to conceive," Dr. Crowley said. "Based on the studies done here, this has now become a treatment choice for one category of infertile women."

Similarly Dr. Crowley has used pulsatile delivery of natural sequence GnRH to induce puberty in men who lack this hormone.

And in one of science's delightful little paradoxes, Dr. Crowley and his colleagues also discovered that GnRH, which has a stimulating effect when applied intermittently, will turn off puberty when applied continuously.

"We've turned this discovery into the treatment of several reproductive disorders, the most notable of which is precocious puberty," Dr. Crowley said. "There are a number of children who have puberty at a very early age with menstrual periods and breast development in 3- and 4-year-old girls and sexual development in boys of the same age. By using long-acting GnRH analogues [chemical derivatives], we can shut off their pituitary and gonads [the testicles in men and ovaries in women] until the time that's proper for them to go through puberty."

This treatment will also slow the growth spurts and rapid skeletal maturation that characterizes this condition.

The marriage of basic laboratory research to direct patient care is an MGH tradition Dr. Crowley said the new center will build on and enhance.

"What the MGH has been unique for in the past is taking clinical observations and explaining them in terms of physiology and pathophysiology, and then using that information to plan a rational treatment for those disorders." said Dr. Crowley, who is also an Associate Professor of Medicine at Harvard Medical School. "That spirit still lives and breathes in the type of research going on here today and is exemplified by this center."

Beginning with Dr. Fuller Albright nearly three generations ago, MGH researchers have described and developed treatments for a number of reproductive disorders over the years.

One of the more famous of these disorders now bears the name of one of Dr. Albright's assistants who first described it: Klinefelter's Syndrome. This testicular disorder results from an extra X chromosome in the male. It is characterized by small testes and sterility.

Other disorders described by MGH researchers include a number of pituitary tumors, adrenal disorders that interfere with ovulation, and various other testicular and ovarian disorders.

Dr. Donahoe, a Professor of Surgery at Harvard Medical School, said the new center will be instrumental in carrying that tradition of reproductive research on into the future.

"It's very important for young investigators who don't have their grants yet to be able to gain access to cores with this level of expertise and consultative advice," Dr. Donahoe said. "This will be a very important tool for faculty growth within the MGH, permitting young investigators to follow an idea wherever it takes him or her." ■

*Core directors of the new Reproductive Endocrine Science Center from left: Dr. Henry T. Keutmann, Dr. Joseph Avruch, Dr. J. Larry Jameson, Dr. Patricia K. Donahoe, and Dr. William F. Crowley.*

# Spaulding Rehabilitation Hospital: Preparing Patients for Living

LAST FALL the MGH saved Richard Vokey's life. This spring Spaulding Rehabilitation Hospital — one of the major affiliated hospitals of the MGH — gave him back that life.

The difference between acute general hospital care and rehabilitative hospital care is more than life and death. It is life and living.

*Richard Vokey (left) of Concord, MA, who suffered a severe head injury last fall, continues to receive speech language pathology from speech therapist Rick Sanders twice a week as an outpatient at Spaulding Rehabilitation Hospital.*

In September 1990 a freak boating accident left Mr. Vokey, a 62-year-old banker from Concord, MA, near death. He had a severed hand, a fractured spine, and severe brain injury.

Surgeons at the MGH replanted (reattached) Mr. Vokey's hand and repaired his spine. After more than 10 speech therapy sessions at the MGH, Mr. Vokey was making early progress toward regaining speech. But he was a long way from holding a conversation. "At that point it was unknown how much speech he'd really recover," Mr. Vokey's wife Maureen said. "It was scary."

The first of April, after two and a half months of occupational and physical therapy as well as speech language pathology at Spaulding, Mr. Vokey attended his first bank board meeting since the accident. Tanned and fit from a week in Florida and talking up a storm, he joked with old friends and thanked them for their support during his ordeal.

"The primary goal I have right now is to get back to work as soon as I can," he said.

Mr. Vokey is a dramatic example of what has become one of the fastest growing segments of medical care — rehabilitation.

While many dozens of acute care hospitals close each year for lack of patients, several dozen rehabilitative hospitals and units open. There are many forces driving this growth: the aging of the population, better medical intervention that has created a larger population capable of being rehabilitated, and the ever-increasing effectiveness of rehabilitation professionals.

"Thirty years ago a patient would have a stroke, and the family would take him home to care for him or place him in a nursing home," said Dr. Manuel J. Lipson, General Director of Spaulding. "This was not only because of the lack of rehabilitation but also because of the lack of medical science."

Today that same stroke patient is likely to go from an acute general hospital like the MGH to a rehabilitation hospital like Spaulding. *Fewer than three percent of Spaulding's patients are discharged to a nursing home. The rest go back to active, busy lives.*

Although rehabilitative care has been around for a hundred years or more, it did not really grow until after the Social Security Acts of 1965 created Medicare and Medicaid. Those health insurance systems, along with other third party insurers, for the first time recognized rehabilitation as reimbursable. By the end of the 1960s, several dozen rehabilitation hospitals, including Spaulding, began.

Originally called the Massachusetts Rehabilitation Hospital, Spaulding opened in 1970. By 1975, 10 floors and 284 beds were available for patients. After principal founder Josiah A. Spaulding's death in 1983, Helen Spaulding assumed the role of interim president and still serves the hospital as a trustee. In 1984 the MGH bought the hospital and renamed it Spaulding Rehabilitation Hospital.

When Spaulding first opened, patients were assigned beds according to vacancy. In 1976 the hospital began grouping patients according to the type of specialized care they needed. By the late 1970s, the hospital had already developed the 13 specialized units it has today.

"Some of the programs developed more quickly than others, but by 1979, we knew these 13 programs were needed — in part because we had a vision and in part because the MGH had a need," Dr. Lipson said. "We were probably five years ahead of the field in this type of super-specialization."

Seeing the need for a high-quality institution that could rehabilitate increasing numbers of patients saved at hospitals like the MGH, the Massachusetts General encouraged Mr. Spaulding to start such an institution.

And because of the large number of stroke patients at the MGH in 1970, stroke rehabilitation became the first specialty at Spaulding. Fracture and amputation units quickly followed. The 13 specialty care areas also include arthritis, spinal cord injury, head injury, cardiac disease, pain, pulmonary disease, cancer, neurological disease, alcoholism and chemical dependency, and pediatrics. In addition to specialization, Spaulding has been in the forefront of many other changes sweeping the field. "We're being referred sicker patients and new types of patients," said Lillian W. Gray, Assistant Administrator of Spaulding. "Thirty years ago a significant head injured population didn't exist — many died at the scene of the accident. Now head injury is a national epidemic. We're also getting people who have had joint replacements, cardiac bypass operations, and even premature babies."

*In August 1989, seven-year-old Rondele "Punky" Miller of Roxbury, MA, was hit by a car and nearly killed. For weeks the youth was hospitalized with a severe head injury at the Massachusetts General Hospital. Surgeons at the MGH finally stabilized Punky's condition so that the child could be transferred to Spaulding Rehabilitation Hospital. After several weeks of intensive therapy at Spaulding, Punky went home on his eighth birthday. Today he is back in school and once again facing a bright future.*

But just as medical technology has greatly increased the numbers of patients who can be rehabilitated, acute care hospitals have been under increasing pressure to discharge patients earlier and earlier.

Likewise rehabilitation hospitals — despite receiving patients earlier, sicker, and with more needs — have also dramatically reduced patient stays.

Twenty years ago a typical stroke patient was a 67-year-old man who spent 25-30 days at the MGH and another 70 days at Spaulding. Today that same stroke patient is 10 years older and comes to Spaulding on the seventh day after his stroke. He stays at Spaulding 35 to 40 days.

"There has been a growing emphasis in rehabilitation on outpatient care," Dr. Lipson said.

In conjunction with this trend, Spaulding opened the Home Health Agency in 1981. Now this service, an MGH/SRH program, provides rehabilitation in the home. SRH also runs satellite programs in Braintree, Hyannis, Medford, and Worcester that provide a range of outpatient therapy services throughout the state.

Another major trend in rehabilitative care has been the move toward outcome research, or "evaluating outcomes."

"Rehabilitation is a difficult field to try and analyze," Dr. Lipson said. "It's hard to quantify. We're trying to look beyond process and whether or not the patient got the medicine or got the therapy, and look at the functional change that resulted from that medicine or that therapy. We want to look at the quality of the outcome."

Training and education will also remain top priorities at Spaulding in coming years. With the support and encouragement of both the Spaulding Hospital trustees and the MGH trustees, Spaulding developed a major educational program about five years ago. "We did this for two reasons," Dr. Lipson said. "First, there is an emerging trend that patients are seeking out the high quality of care created by teaching hospitals. And second, the MGH has a 180-year tradition of teaching."

Over the last five years Spaulding has established 11 fellowship or residency positions. In addition the hospital is submitting an application to become a residency training program center for rehabilitation. "That's an important designation because then we would become a teaching hospital in our own right," Dr. Lipson said.

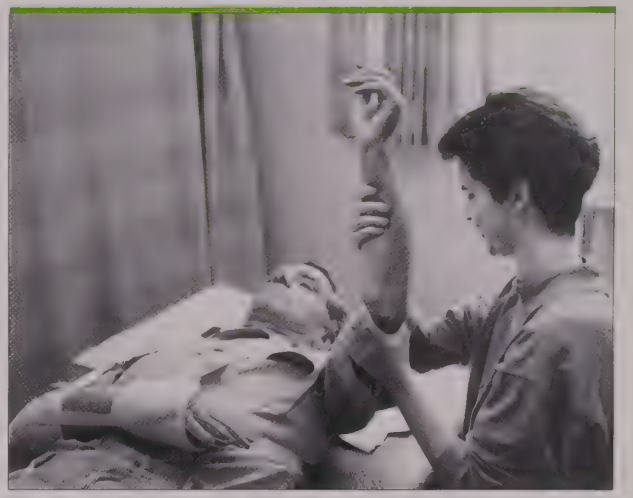
Although Spaulding is a major affiliate of and shares many services with the MGH, it is not solely dependent on its sister hospital for either patients or teaching ties. In fact only about one-third of Spaulding's 3,000 patients each year are referred by MGH physicians. Some 100 hospitals throughout New England send patients to Spaulding. In addition to its affiliation with the MGH and Harvard Medical School, Spaulding is also associated with Tufts Medical School.

*Already the largest rehabilitation hospital in the United States, Spaulding will soon expand further with the opening of a new 40,000 square foot addition, the second phase of a 10-year capital expansion program.*

The addition will provide much-needed therapy space for the hospital's 284 inpatients and large outpatient population. Among the unique features of the new addition will be a fully furnished apartment where patients can be evaluated for and learn home skills in a realistic setting. Spaulding will also soon become the only rehabilitation hospital in the world with a pier for its patients.

"A person may do very well in a quiet room," Ms. Gray said. "But not very well under a lot of distractions and noise. The pier will be one of those tests when a patient is taken outdoors for the first time. We may even have a sailboat for the patients."

At Spaulding the emphasis has always been on preparing patients for living, not just for life. ■



*Physical therapist Liz Phelan works with Richard Vokey's good arm to try and restore more strength and mobility to the limb.*

## —Dr. Harlow

*(Continued from Page 1)*

Charlestown.

"With the collection of young scientists already at the MGH Cancer Center and the chance to bring in a number of others, we have the opportunity to put together a very strong unit," Dr. Harlow said. "That environment is already starting to come together."

Not surprisingly, a major emphasis of the new laboratory will be on so-called tumor suppressor genes and their role in human tumors. The tumor suppressor field is rapidly gaining prominence in cancer research laboratories worldwide as a result of Dr. Harlow's revolutionary discovery.

Over the last 20 years scientists have learned much about how a normal cell is transformed into a cancer cell.

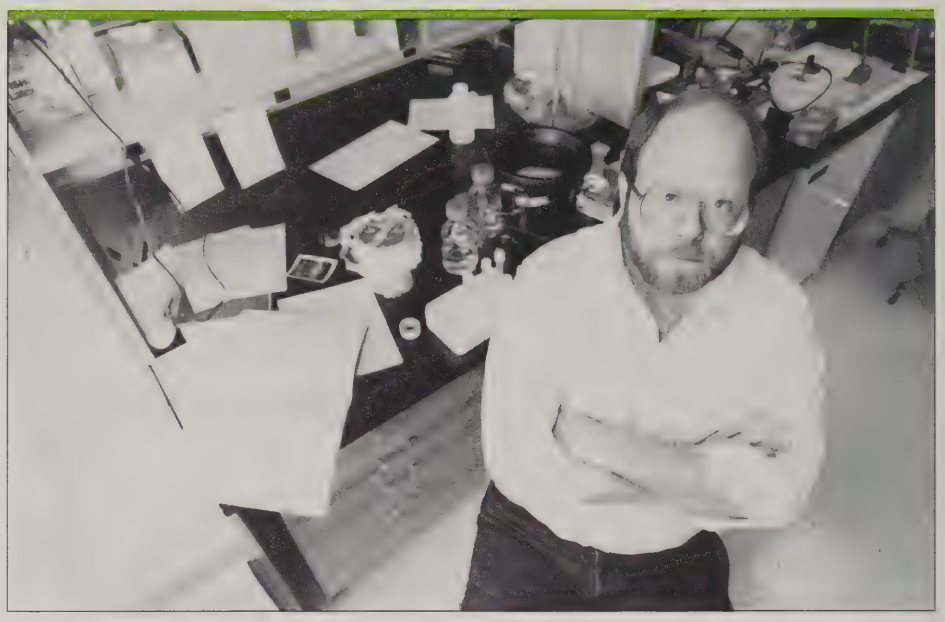
Cells are born by dividing, growing, and dividing again. Every minute about 10 million cells divide in the human body. Cells divide on schedule in a controlled fashion. New cells replace old ones or perform new tasks. When the skin is cut, for example, chemical signals tell the surrounding cells to divide and grow faster, replacing the damaged cells. When the wound is healed, other chemical signals tell the new cells to stop dividing and return to a normal cell cycle.

But this delicate balance of cell growth can be disturbed in many ways. When cells divide and multiply uncontrollably — this is cancer.

Beginning about 20 years ago, cancer researchers identified two groups of genes (units of inheritance) that contribute to cancer growth.

An oncogene (a single altered gene) can speed up the cell cycle when the oncogene's normal growth-producing signals are altered. These so-called cancer "accelerators" or positive-acting genes can transform a normal human cell into a cancer cell.

Tumor suppressor genes, on the other hand, are negative-acting genes. They can also lead to cancer but only by their absence. Their activity seems to inhibit or prevent cancerous growth. "They act like the brakes holding a heavy truck on a hill," Dr. Harlow said. "If the brakes suddenly fail, the truck rolls down the hill out of control. If the tumor suppressor genes fail, the cell divides out of control."



*Dr. Harlow in the newly formed Laboratory of Molecular Oncology at the MGH Cancer Center*

Until recently scientists thought the two systems of cancer accelerators and cancer brakes functioned independently. And most considered oncogenes to be the more important players in the elaborate cancer drama.

"If you asked everybody five years ago which group of genes was more important in causing human tumors, I think everybody would have said, 'oncogenes, definitely,'" Dr. Harlow said. "But I think the honest answer is that it's a combination of both."

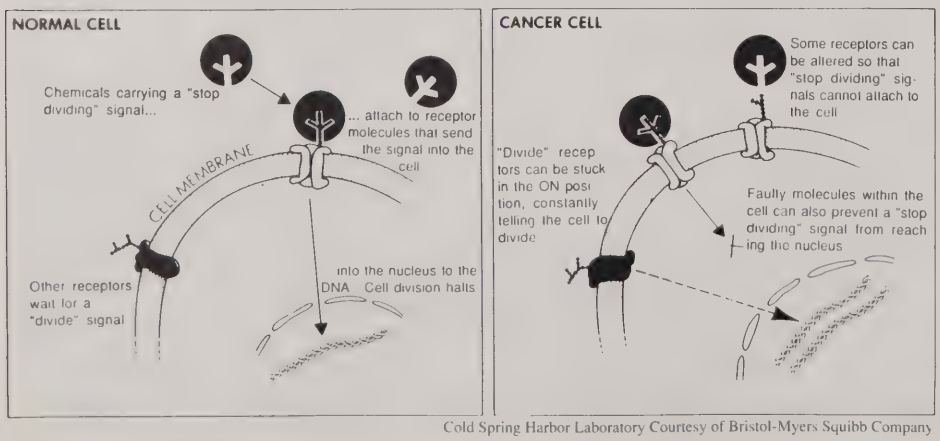
Dr. Harlow's unexpected discovery in 1988 of a definite link between the two systems has not only united the two independent lines of scientific investigation but also shifted investigators' attention to the tumor suppressor field.

"I don't know of any tumors that have shown up with no tumor suppressor genes being associated with them," Dr. Harlow said. "For normal growth you need both an accelerator and a brake. It would be difficult to control a car with the accelerator alone, but if you just had a brake, you could never go at all. So I think it's clear you are going to need to have both types of changes — the accelerators and the brakes being broken — to be able to make a tumor cell."

Dr. Harlow uncovered just such a dual breakdown in the summer of 1988. Specifically, he found that a protein (E1A) produced by a virus oncogene binds with and disables one of a cell's normal cancer-suppressing proteins. This brake protein ordinarily inhibits the development of retinoblastoma, an eye cancer found in children. Without the action of the brake, retinoblastoma develops.

Dr. Harlow found that the protein produced by the retinoblastoma gene gets "trapped" by the virus protein. This interaction mimics the cancer-causing effects of a mutation or change. The discovery of a direct connection between positive and negative cancer factors raises an exciting new possibility for the action of tumor viruses — that is, the positive may work by turning off the negative.

"We don't really know yet how they interact," said Dr. Harlow, who earlier this spring received for the discovery the 14th annual Bristol-Myers Squibb Award for Distinguished Achievement in Cancer Research. "That's the next step. We want to look for the same relationship in other tumor suppressing genes. We don't know that it's going to happen more often, but at


NORMAL CELL
Chemicals carrying a "stop dividing" signal...
... attach to receptor molecules that send the signal into the cell
CELL MEMBRANE
Other receptors wait for a "divide" signal
into the nucleus to the DNA. Cell division halts
CANCER CELL
Some receptors can be altered so that "stop dividing" signals cannot attach to the cell
"Divide" receptors can be stuck in the ON position, constantly telling the cell to divide
Faulty molecules within the cell can also prevent a "stop dividing" signal from reaching the nucleus

Cold Spring Harbor Laboratory Courtesy of Bristol-Myers Squibb Company

# *MGH Recruiting Minorities to Enter Research, Academics*

TO TAMARA CALLAHAN, becoming a doctor meant taking care of patients.

"I never thought of myself as doing research or going into academics," said Ms. Callahan, a second-year student at Harvard Medical School. "I came here thinking of medicine as a clinical profession — wearing a white coat, seeing patients all day long."

After spending last summer in a white coat of a different kind — a white laboratory coat — working on a research project in an MGH lab, Ms. Callahan has a much different view of her chosen profession.

"For the first time I realized I could have it all — patients, research, academics, everything," Ms. Callahan said. "The experience really gave me a new perspective on all the possibilities there are in medicine."

Ms. Callahan was part of a unique pilot program begun last summer by the MGH Medical Services to increase the numbers of minorities in research and academic positions in medicine. Instead of spending their summers at the beach or working in unrelated jobs, the eight college and medical students saw a side of medicine many never knew existed.

Although African Americans, Hispanics, and American Indians make up 9.3 percent of total medical school enrollment, they account for only 3.5 percent of medical school faculty, according to 1990 figures compiled by the Association of American Medical Colleges. Recognizing the imbalance that exists not only in teaching but also in research, the MGH Medical Services formed a Minority Recruitment Committee (MRC) in 1987 to encourage more minority students to consider a career in these fields.

"There is no guarantee that anyone we help to train will then use that training to help specific minority health issues," said Dr. Anthony Coles, chairman of the MRC. "We hope they will but beyond that I think it's important to provide minorities the same opportunities, professionally and socially, as nonminorities."

"One of the reasons the MGH has become a great national resource over the years is because it has led the way in important commitments to society and to patient care," added Dr. John Potts, Physician-in-Chief of Medical Services. "Increasing minority opportunities at the hospital is one of those commitments."

Although the MGH minority recruitment effort has attracted national attention, its beginnings were modest. When the program began in 1987, the primary recruiting focus was Harvard Medical School. "As the program blossomed, it became clear that the only real potential for growth was to start recruiting from medical schools besides just Harvard," Dr. Coles said. "It also became clear very early on that we had to attract students earlier in their careers — before they got to medical school. There was the recognition that the pre-med students of today are going to be

*(Concluded on Page 8)*

*Dr. Anthony Coles (left), Chairman of the MGH Minority Recruitment Committee, and Dr. John Potts, Physician-in-Chief of Medical Services, discuss plans for this summer's high school trainee program that will bring minority high school students into MGH laboratories to work side-by-side hospital investigators.*

least it opens up the possibility."

Dr. Stephen H. Friend, a member of the MGH Cancer Center, cloned the retinoblastoma gene in 1988 while at the Massachusetts Institute of Technology. The RB gene was the first of the tumor suppressor genes to be isolated and reproduced in the laboratory. Mutations of the RB gene have also been found in lung cancers. Tumor suppressing genes are also turning up in many other types of cancer, including breast and colon cancer. "So far there are probably six or seven tumor suppressing genes that have been actually cloned but there will be many, many more," Dr. Harlow said.

Although the unexpected discovery dramatically uniting the two lines of independent investigation has caused great excitement in the scientific community, Dr. Harlow stressed that the impact of the finding will not be felt outside the laboratory for many years.

"Over the last 15 years we have accomplished an unbelievable expansion of our knowledge about how cells decide when to divide and when not to divide. This discovery is one more step in that process, but we still have so much more to learn," said Dr. Harlow, who has also been appointed Professor of Genetics at Harvard Medical School.

"What I'd like to know now is how the retinoblastoma protein actually functions. What role does it play in the cell? And how does the viral protein change that role? I'd also like to know who the other proteins are that bind to the virus protein E1A. Who are they? How do they work? How do they contribute to telling a cell when to divide and when not to divide?"

After unraveling a twisted plot extending back through nearly two decades of cancer research, Dr. Harlow says it is now time to begin the next act. ■

## — Minority Recruitment Program: "Building a Better Institution"

*(Concluded from Page 7)*

the physicians of tomorrow. So if we wanted to have any impact on future physicians, we had to start with today's pre-med students."

At the same time the MRC was expanding its focus beyond Harvard, it was also gaining admirers. Last year Merck, Sharp & Dohme Research Laboratories contributed $75,000 over three years to support the Summer Research Trainee Program at MGH.

The summer research program offers medical and college students the opportunity to spend 8 to 12 weeks of the summer working in an MGH laboratory on a research project of their choosing. "The program is tailored to the level of experience of each of the students," Dr. Coles said. The program, which is headed by Dr. Conrad Smith, a cardiology fellow at the MGH, is an all-volunteer effort. "It's really a team effort," Dr. Coles said. Students receive a $3,000 stipend and once-in-a-lifetime experience.

"It was a fabulous experience," Ms. Callahan said. "The people I worked with did a great job of making sure I was exposed to everything."

From 8 students last year, the Summer Research Trainee Program has expanded to 20 this year. In addition two alumni will be eligible for the Merck/MGH Fellowship Award. This includes a $10,000 award plus living stipend to support a summer of research the following year at Merck laboratories in Rahway, NJ.

"The next focus will be on high school students," Dr. Coles said. "We feel if we really want to have the most impact, we have to identify students and generate interest as early as we can."

The high school program, which is being supported by a $30,000 grant from the National Institutes of Health, will be run in cooperation with the MGH Division of Research Affairs. It will bring 10 high school students and two advisers into MGH laboratories this summer to work side-by-side hospital investigators. Over the school year the students and their two high school advisers will continue to meet, using the experience they gain over the summer to try and solve a predefined research problem.

"It's important for high school students to do as much learning as possible at this stage of their lives," Dr. Coles said. "That's why we want to provide an educational approach with a defined curriculum, as well as an internship program."

"We want to encourage more minority students to seek the long path of educational achievement," Dr. Potts said. "We want to do this by example and by exposure. Our goal is to make this a demonstration project that has national impact."

Ultimately Dr. Coles said the goal of the recruitment program is not to increase the numbers of minority medical students. "That's the job of the medical schools," he said. "We're concerned with increasing the choices and opportunities open to minority medical students. And that's where we think the MGH can make a difference."

And that difference, Dr. Potts said, affects the hospital as much as it does the lives of many dozen minority students.

"These young people have brought talent, commitment, energy, and ideas with them," Dr. Potts said. "Their activities have led to an unstated bond that now exists among us. We're a better institution because of them." ■

*Tamara Callahan (left), a Harvard Medical School student, confers with her supervisor Dr. Janet Hall.*

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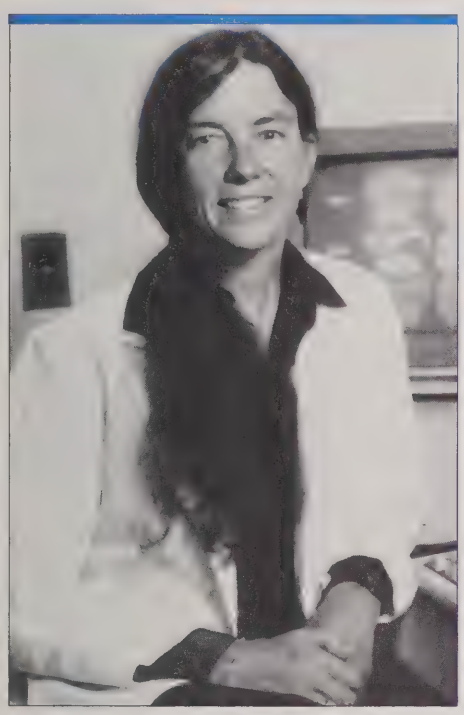

*Dr. Anne B. Young*

# Neurologist Anne B. Young Named First Woman Service Chief

WHEN neurologist Anne B. Young, MD, PhD, hung out her shingle in 1978, she knew she was interested in Huntington's, Parkinson's, and Alzheimer's diseases — "I just didn't know I would end up being THAT interested," she said.

But that is the way Dr. Young's medical career has gone. Each new patient, each new discovery in the laboratory has been like a good book — impossible to put down once she opened the cover. How much more interesting can it get?

Dr. Young will soon find out. Later this summer she begins a new chapter in her own career and at the same time turns the page on 180 years of history at the MGH.

On August 1 Dr. Young will become Chief of Neurology at the MGH, the first woman Chief of Service at the 180-year-old hospital, and the first female Chief of Neurology at a U.S. teaching hospital.

The appointment reunites Dr. Young, a specialist in movement disorders, with a number of already long-time MGH colleagues.

In 1983 Dr. Young, a Professor of Neurology at the University of Michigan, and James F. Gusella, PhD, Director of the MGH Molecular Neurogenetics Laboratory, were part of a team of investigators who discovered a genetic "marker" for Huntington's disease, a fatal hereditary disorder causing involuntary movements and mental deterioration.

A marker is a piece of DNA that exhibits the same pattern of inheritance as a gene. Although scientists have not yet found the gene responsible for Huntington's disease, the marker allows them to determine who carries the defective gene and will allow them to find the gene itself and begin work on a cure.

In addition to her work on Huntington's disease, Dr. Young is also an expert on Alzheimer's disease. She has spent the last several years investigating a brain chemical called glutamic acid and its role as a possible culprit in Alzheimer's disease. Dr. Young's work on glutamic acid parallels research taking place at the MGH. A group of MGH scientists headed by Dr. M. Flint Beal, Director of the Neurochemistry

*(Continued on Page 6)*

## *Durability Improving for Artificial Hip Recipients*

IMAGINE a machine that could withstand 600 pounds of load a million times a year for 10 years, had a range of motion of 90 degrees, and never needed oil.

Sound impossible?

Meet the artificial hip joint.

Since its introduction in 1962, total hip replacement surgery has become the most common total joint replacement operation in the world. Some 250,000 people every year undergo the procedure to alleviate the pain and disability of severe arthritis.

For most, the operation has meant a dramatic improvement in their quality of life. Patients once unable to walk or even sit without pain now play golf, swim, even ride a bicycle, without pain or discomfort.

But as time went on and recipients continued to live longer and expect more from their replacement joints, an increasing number of patients experienced loosening of their implants. "It's really not surprising so many of the early patients had loosening problems," said Dr. William H. Harris, Chief of the MGH Hip and Implant Service. "In ordinary walking, a person bears about three times his body weight on each hip. And that can easily get up to 5, 7, or even 10 times a person's body weight if the person is at all vigorous. So the physical demands on

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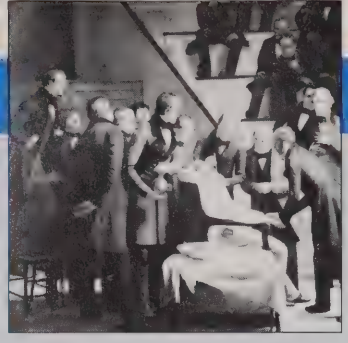

# Coming of Age In the United States

ONE HUNDRED AND EIGHTY YEARS is a long time without a woman chief of service. As a page 1 article describes, on August 1 Anne Buckingham Young will become MGH Chief of Neurology. At the same time the MGH will become the first teaching hospital in the United States to have a woman chief of neurology.

It was not too many years ago that few American women went to medical school. When they did become doctors, they were channeled into specialties that are "suited for them."

After starting her training here at the MGH in 1949, one woman was courageous enough to defy convention and became a surgeon. Anne Wight Phillips had few woman counterparts across the country and fewer still when she became a burn specialist. To a great extent neurology in the United States has also been a male club. Considered one of the most cerebral branches of medicine, neurology has become one of the most challenging frontiers remaining. In this background Dr. Young's achievement is all the more outstanding. She is regarded as one of the great patient care, research, and teaching leaders in her field. In short she is clearly the best person for the position.

• • •

SCARCELY had Dr. Young's appointment been announced when the MGH had a second woman Chief of Service. The Chief of Pediatric Surgery, a position that Dr. Patricia Kilroy Donahoe has occupied since 1984, has been elevated at the MGH to the status of service chief.

An MGH pediatric surgeon since 1970, Dr. Donahoe has also proved herself extraordinary in patient care, research, and teaching. She carries out a wide range of chest (thoracic), urological, and abdominal surgical procedures, for which she is nationally known. Her basic and clinical research with what is called Müllerian Inhibiting Substance is also nationally known and being developed for the treatment of ovarian cancer. She teaches at Harvard Medical School and advises Harvard-MIT Health Science Technology students. Both Drs. Donahoe and Young have combined their arduous and time-consuming academic careers with raising children.

It is obvious that medicine is far from the only profession that has been slow to choose women as leaders. In most professions men still dominate the choice positions, especially at the more prestigious organizations. The appointments of Drs. Young and Donahoe are encouraging. Very encouraging! ■

## —*Artificial Hip Joint*

*(Continued from Page 1)*

the hip are extraordinarily high."

By the early 1970s, the incidence of loosening was as high as 24 percent at some hospitals five years after surgery. By 10 years those numbers had climbed to 44 percent.

"The figures were very alarming," Dr. Harris said. "During the 1970s and much of the 80s, there was a period of great consternation, confusion, and reassessment by the orthopedic community."

Today, thanks in large part to pioneering work done in the MGH Orthopaedic Biomechanics Laboratory, loosening no longer poses a serious problem for most artificial hip recipients.

Instead it is a commentary on the ever-increasing life expectancy that "wear" of the artificial parts has now become the number one problem facing long-term survivors of total hip replacement surgery.

In a total hip replacement, surgeons remove the ball of the ball-and-socket joint and replace it with a smaller metal ball attached to a stem. The stem is inserted into the marrow cavity of the femur (thigh bone).

Surgeons replace the socket (acetabulum) with a layer of special plastic called high-density polyethylene. The polyethylene, which has tremendous strength, a very low level of friction, and excellent compatibility with living tissues, becomes the weight-bearing surface of the new joint.

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Either of these two artificial parts — the metal ball with its stem or the plastic socket — can be attached to the skeleton in one of two ways — with or without cement.

Bone cement is actually an acrylic plastic. Engineers use this same compound to make taillight covers on cars. Surgeons use it to fix artificial joints in place. The putty-like cement is packed into the bone, and the artificial part inserted. The cement hardens in about 12 to 15 minutes.

*Dr. William H. Harris, Chief of the MGH Hip and Implant Service, examines an Xray of a cadaver femur which is going to be used for biomechanical testing.*

The chief alternative to cement is called bony ingrowth. In this method the patient's own bone grows into pores on the surface of the artificial part.

"During the decade of the 80s there was a major difference of opinion between using cement and cement-less techniques," Dr. Harris said.

Over the past few years, researchers in the MGH Biomechanics Laboratory have helped resolve that debate. Through autopsy retrieval studies pioneered at the MGH, researchers were able to pinpoint how and when loosening began and then to develop new techniques to correct the problems.

For discoveries in the laboratory, Dr. Harris and his group have won eight national awards in orthopedic research.

Investigators have developed a number of different methods to study component loosening in artificial joint replacements.

"But without question the most revealing and most important method is autopsy-retrieved material from successful total hip replacements," Dr. Harris said. "If you wait until somebody's already failed, had symptoms and enough trouble to be operated on, a whole lot of secondary changes have taken place. You don't know what started the process of loosening. But if you can take someone whose implant was functioning well and who died for some other reason, then you have an opportunity to study any changes when they first started — before they became symptomatic."

Through autopsy studies of hips willed to him by former patients, Dr. Harris and his group determined that the mechanism that causes failure is not the same for each side of the joint. Loosening on the femur side was mechanical in origin and on the socket side biologic in origin.

On the thigh piece, loosening occurs because the cement "debonds" or separates from the metal.

"This is exactly opposite of what everyone had thought," Dr. Harris said. "We and everybody else thought the problem started with the cement-bone interface. It doesn't. The problem lies with the cement-metal interface."

Armed with this information from the laboratory, surgeons were able to modify their operating room techniques to make the cement-metal bond stronger.

First the metal was precoated with a layer of bone cement and roughened to reduce its ability to slip. Then surgeons made the cement stronger by mixing it under a vacuum to make it less porous. By getting rid of the air bubbles, Dr. Harris said they have been able to make the cement five times stronger.

Although long-term numbers are still needed on the latest techniques, the improvement in femoral loosening is impressive.

"Ninety-seven percent of the femoral components are now solidly fixed at 11 years," Dr. Harris said. "And that's a dramatic and tremendous difference."

Because of these excellent outcomes and the increasing life expectancy of patients, Dr. Harris said the major long-term problem facing artificial hip recipients has shifted from loosening to "wear."

From autopsy studies, Dr. Harris and his group determined that small particles of the polyethylene get in behind the socket. This debris prompts macrophages (a cell of the immune system) to congregate in the area. The macrophages try to digest the artificial particles, cannot, and in the process, wind up producing enzymes capable of eating bone.

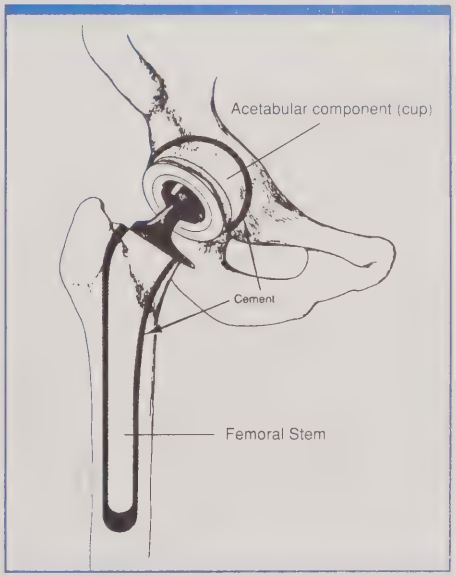
"The polyethylene does an extraordinarily good job, but it doesn't do it well enough," Dr. Harris said. "The problem is the demands we're putting on this thing are so very high. And over time — often 10, 12, 15 years, but sometimes sooner than that — the polyethylene begins to wear and you get the small particles."

Originally Sir John Charnley, who pioneered the operation in 1962, used teflon for the socket. "It had a very low friction coefficient but the problem was, it wore out in two years," Dr. Harris said.

Sir John had 300 consecutive failures with the teflon before turning to the high-density polyethylene which surgeons have used ever since.

Although the loosening mechanism is biologic on the socket side, Dr. Harris believes the solution to the problem of wear debris will be mechanical.

"The problem with trying to shut off the immune response to the debris is that that same response is needed elsewhere in the body for a whole variety of other things," Dr. Harris said. "I think a better material is more likely. People are already working on ceramics and metals as possible alternatives."




As recipients continue to live longer and lead more active lives, increasing the life expectancy of a total hip replacement remains a top priority of Dr. Harris and his group.

"In the early days we were delighted to have 3-year data or 5-year data because it was better than anything that had existed before," said Dr. Harris, who is also a Clinical Professor of Orthopaedic Surgery at Harvard Medical School. "But now we've got to be going longer than 10 years because the people we're treating are living longer. The life expectancy of a 60-year-old is 15 to 17 years. That's a very demanding statistic." ■

# *The Institute of Health Professions:*

# *A Good Idea Come to Life*

THE WHOLE IDEA behind the MGH-Institute of Health Professions (IHP), Patrick E. McCarthy was explaining, *is* ideas.

"It's what I call 'convening,'" said Mr. McCarthy, President of the IHP, the educational affiliate of the MGH. "If you are part of the family of institutions that make up the MGH, then you have a unique responsibility to bring people together around ideas."

The IHP has been bringing people — students, health care professionals, faculty, patients, scientists, and members of the community — together around ideas since 1977.

The idea can be as simple as a dietetics student studying whether bran might be a more effective and cheaper substitute for the laxatives given elderly residents of a nursing home.

The idea can be as far-ranging as a two-day, national conference on children with dyslexia.

Or the idea can be as varied as an MGH-IHP lecture series on medical ethics.

"There is a natural symbiosis [mutually beneficial relationship] and a designed symbiosis between the IHP and the MGH, be it in education, in research, or in the convening of ideas," Mr. McCarthy said.

This "symbiosis" makes the Institute of Health Professions one of the unique graduate schools in the country. The IHP is unusual, if not unique, for many reasons: It is a graduate school without an undergraduate university; it is affiliated with a hospital rather than a university or medical school; it is comparatively small (300 students); it is sharply focused (four disciplines); and in an age of crisis in higher education, it is very self-assured.

"We couldn't do what we're doing anywhere else," said Mary Carey, PhD, Director of the Graduate Program in Dietetics. "Because anywhere else we wouldn't be part of the MGH."

The IHP was founded in 1977 with graduate degree-granting authority in four professions — speech language pathology, nursing, dietetics, and physical therapy. *This fall the Institute will admit students into its master's program in speech language pathology.* The IHP also operates a Program in Ethics.

*IHP nursing student Eileen Scaringi*

As at MGH, research is a major emphasis at the Institute. All students must write a thesis; many graduate with one or more professional publications to their credit.

The newest program in speech language pathology is an example both of the emphasis placed on research at the IHP and of the unique relationship between the Institute and the MGH.

The speech program evolved out of the Neurolinguistics Laboratory established by the Institute in 1983.

"The program actually developed backwards but in the most delightful way," said John L. Locke, PhD, Director of the academic program and of the Neurolinguistics Laboratory. "We've always had the patient component with the Speech Pathology Department at the hospital. Then we developed the research component. And now we have the academic component."

***From left to right:*** *Lillian Sonnenberg, IHP Adjunct Assistant Professor, and dietetics students Megan Duke and Isabel Vazquez-Rivera.*

And as the final piece of the program, the academic portion will be designed around the already well-established patient and research components.

"So the central thrust of the academic program will be on language problems associated either with brain damage or with nonorthodox brain structure," Dr. Locke said. "In dyslexia, stuttering, and other developmental language disorders, the brain usually is not damaged, but there is likely to be something different about the way it was put together."

Increasing the emphasis on research in all the programs is a continuing goal of the IHP.

"If you're going to be on the cutting edge of any professional education you need to be adding to the body of knowledge as well as simply distributing what already exists," noted Lydia Wingate, PhD, Director of the Graduate Program in Physical Therapy.

Every student in PT must complete a research project as part of the thesis requirement. Many of the projects end up as published articles. One recent graduate, for instance, has published an article comparing old and young people rising from sitting to standing; another PT graduate received an award from the Pediatrics Section of the American PT Association for her study of strength measurement in healthy children and children with Duchenne muscular dystrophy. Still another PT graduate, now an associate professor in Fresno, California, has published several articles related to the ankle.

"Every research project relates to a clinical problem," Dr. Wingate said.

Two years ago the Institute received a $1 million gift from the Amelia Peabody Charitable Trust to establish an endowed chair in Nursing Research. "We want to bring a nationally renowned researcher in nursing to the Institute," said Elizabeth M. Grady, PhD, Director of the Graduate Program in Nursing. "There is an evolving emphasis on research within the nursing discipline. This chair will allow us to compete on the leading edge of that trend."

The Amelia Peabody Chair in Nursing Research will be the second endowed chair at the Institute. In 1987 two major gifts helped establish the Henry Knox Sherrill Professorship in Ethics. That chair was named in memory of the late Rev. Henry Knox Sherrill, former Presiding Bishop of the Protestant Episcopal Church and Chairman of the MGH Board of Trustees. The holder of the chair also holds the joint appointment of Ethicist-in-Residence at the MGH and provides consultation on patient care, research, and policy issues.

*Speech language pathologist Sharon Nellis McLean works with a stroke patient at Spaulding Rehabilitation Hospital.*

The two institutions share many other facilities, programs, interests, and goals. The MGH provides patients for internship and research projects, mentors for students, laboratories, libraries, and what Dr. Carey calls "a reality check."

"Sometimes you'd like to solve the world's problems, but you don't have the reality base to know how to go about it in your first research effort," Dr. Carey said. "The MGH has the patients, researchers, and health care professionals who can help you not only to understand those problems but also bring the reality to them."

In addition to research the Institute will also be emphasizing management training in coming years. "We are very interested in fulfilling the prophecy that our graduates are going to be leaders," Mr. McCarthy said. "To that end we feel very strongly that we need to pay specific attention to the management requirements of that leadership."

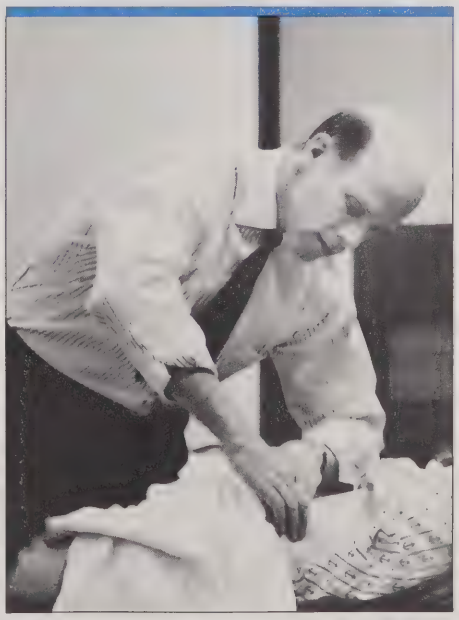
Currently the IHP is discussing various options with a number of well-known university management programs in the Boston area. "Our dilemma is, Do we set up a separate track in management in the health professions? Or do we build management into the curriculum for all our programs? That hasn't been answered yet," Mr. McCarthy said.

Adding more programs simply for the sake of adding more programs, however, is definitely not a goal. "In terms of growth, we're concentrating really on two areas — growing quality in the fields we're already in, and deciding on specialties in fields that surround us."

Adding fellowship programs would be one way of accomplishing these goals; developing cooperative programs with other departments of the MGH is another. "It's important to remember that the spirit of the Institute is modest," Mr. McCarthy said. "We hope we're large in quality, but we're small in size, and we want to stay that way."

That small size, however, has never stopped the Institute from thinking big. And increasing the number and quality of its educational forums and conferences aimed at the general public is a goal of all the programs. This year the dietetics program has begun a three-part series of courses on "Women and Nutrition" aimed at people outside of dietetics. In April the Center for Reading and Writing Research, part of the speech language pathology program, held a two-day conference with the Landmark School in Manchester, MA, for parents of dyslexic children. Two years ago the Institute, with the leadership of the physical therapy program, forged a collaborative agreement with the world-famous Karolinska Institute in Stockholm, Sweden, to set up faculty and student exchanges and joint research projects. This year the nursing program offered a one-day "AIDS Clinical Update" open to all the affiliates of the MGH.

"Ultimately our aim is not to grow in some crazy fashion," Mr. McCarthy said. "But rather to grow carefully in a quality conscious fashion." ■



*Dan Dyrek, IHP Assistant Professor of Physical Therapy*

# — Dr. Anne B. Young Named Neurology Chief

*(Continued from Page 1)*

Laboratory, and Dr. Neil W. Kowall, Director of the Experimental Neuropathology Laboratory, is also investigating the role of glutamic acid in Alzheimer's and also Huntington's disease.

Dr. Young's interest in positron emission tomography (PET) scanning will also relocate well to the MGH. One of her major interests has been the application of high technology to neurology. The MGH is one of only several dozen institutions in the world with a major PET center. The technology allows doctors to view uniquely the status of blood flow and other body functions. Dr. Young, who in addition to an MD also has a PhD in pharmacology (the study of the actions of drugs), has spent several years investigating new compounds to image drug receptors on brain tumors and in normal brains with PET technology.

"The reason I got the two degrees was so I could apply my love for science to studies of human disease," Dr. Young said. "For me the most exciting thing about medicine is the interaction between what I learn from my patients and what I am doing in the laboratory."

That interaction prompted her to move to Michigan in 1978 and specialize in Huntington's disease and other movement disorders — even though at the time she had seen only one patient with Huntington's.

"He was a middle-aged man, sort of a drifter, but he had an incredible impact on me," Dr. Young said. "His symptoms were still quite moderate so that he was very conversant about the impact that the disease had had on him and on his family. I was also very impressed by the movements.

"I've always been interested in how people move; how the normal brain coordinates movement. And then there are all these diseases that affect pretty much the same area of the brain but have totally opposite effects on movement.

"So I've always been fascinated about what makes a person with Huntington's disease different from a person with Parkinson's disease, or with dystonia."

At Michigan she co-directed the university's Movement Disorders Clinic with her husband, Dr. John B. Penney, Jr. Dr. Penney, also a specialist in movement disorders with a primary interest in Parkinson's disease, has been appointed a neurologist at the MGH and Professor of Neurology at Harvard Medical School.

Through their patients at Michigan, Drs. Young and Penney met Nancy Wexler, PhD. Dr. Wexler, a graduate of Michigan, was organizing the so-called "Venezuelan Project." The project brought together geneticists, neurologists, psychologists, nurses, anthropologists, historians, and photographers, who travel to Venezuela each spring to collect tissue and blood samples and to make neurological evaluations of a large Venezuelan family. The family includes more than 11,000 descendants of a woman who had Huntington's disease and lived more than a century ago.

Within two years of the start of the project in 1981, the investigators, who included Dr. Gusella of the MGH, found a marker gene for the deadly disease. Dr. Gusella was the principal author of the landmark paper reporting the finding in the journal *Nature*.

The only member of the original team, besides Dr. Wexler, to return to Venezuela every year, Dr. Young, with four other neurologists, performs more than 700 neurological exams each year on the Venezuelan family.

"Every new diagnosis we make gets us that much closer to the gene," said Dr. Young, who because of her Venezuelan work is considered one of the foremost experts in the world on the early diagnosis of Huntington's. In addition to her work on brain tumors, Dr. Young has also pioneered the use of PET scanning techniques for the early diagnosis of Huntington's disease and other neurological dosorders.

In the laboratory Dr. Young is also studying how the brain normally controls movement and how the brain is damaged in diseases such as Alzheimer's, Parkinson's, epilepsy, dystonia, Tourette's Syndrome, and others. At Michigan she was Program Director of the Alzheimer's Disease Research Center, one of only 15 Alzheimer's research centers in the country.

"Our theory in Alzheimer's disease is that our own brain may contain toxic substances," Dr. Young said.

## Dr. Young Replaces A Former Colleague

*Dr. Joseph B. Martin*

INCOMING Neurology Chief Anne B. Young, MD, PhD, replaces a former colleague and pioneer in the study of degenerative neurological diseases.

Former Neurology Chief Joseph B. Martin, MD, PhD, left the MGH July 1, 1989, to become Dean of the School of Medicine at the University of California at San Francisco. He was MGH Chief of Neurology for 11 years. During that time Dr. Martin guided the Neurology Service into one of the premier departments in the country. Dr. Martin's own personal interest was the study of inherited diseases.

In 1983 he joined his later successor, Dr. Young, and another MGH colleague, James F. Gusella, PhD, Director of the Molecular Neurogenetics Laboratory, in the so-called "Venezuelan Project." The members of that project discovered a "marker" linked to the gene for Huntington's disease, an inherited, fatal disorder that causes involuntary movements and mental incapacitation. The marker helped researchers develop a test to determine who of the 150,000 Americans at-risk for the disease are carriers of the defective gene.

The strategy of "gene linkage" members used to find the Huntington's marker was a breakthrough. Dr. Gusella and his colleagues at the MGH have since used gene linkage techniques to find markers for several other inherited diseases.

A specialist in neuroendocrinology and neuropeptides, Dr. Martin was the first holder of the Julieanne Dorn Professor of Neurology Chair at Harvard Medical School. The chair was established in 1981 to support research at the MGH in genetic disorders of the nervous systems. Dr. Young will assume the Professorship along with her other duties.

In addition to his many contributions to neurology at the MGH, Dr. Martin also served as Chairman of the MGH General Executive Committee. In 1981 the MGH Board of Trustees named him interim General Director of the hospital during the search which resulted in the appointment of the current General Director, Dr. J. Robert Buchanan.

Dr. Verne S. Caviness, Chief of Pediatric Neurology, will remain Acting Chief of Neurology until Dr. Young's appointment becomes effective August 1. Dr. Caviness is also Joseph and Rose Kennedy Professor of Child Neurology and Mental Retardation at Harvard Medical School. ■

One of these toxins may be glutamic acid, a neurotransmitter (chemical messenger) normally found and needed in the brain.

"But some of these normal neurotransmitters, particularly glutamic acid, may be toxic to neurons under certain conditions," Dr. Young said.

Scientists already know that most of the types of nerve cells that die in the course of Alzheimer's disease either use glutamic acid or similar chemicals as messengers, or connect with other nerve cells that do.

"It may be that the glutamic acid itself does not become abnormal, but that the cells may not respond to it normally because of a genetic defect or because of some other process that's going on in the cell body," Dr. Young said. "And therefore the glutamic acid that wasn't toxic before becomes toxic."

Dr. Young is anxious to continue at the MGH her work on Huntington's and Alzheimer's diseases and the role of glutamic acid. There Dr. Beal, Dr. Kowall, and others are pursuing some of the same issues.

Fostering collaborations — whether between doctors and patients in the clinic, neurologists and radiologists in the PET center, or scientists and doctors in the laboratory — is the primary goal of Dr. Young at the MGH.

To this end she has three primary objectives: Develop more subspecialty clinics to serve the general public, general practitioners, and neurologists; organize a coalition of laboratories that will bring all the many scientists working on basic research projects in neurology at the hospital closer together, and coordinate all of the many interactions between these various parts.

"All of the people at the MGH are really outstanding — both the clinicians and the basic scientists," Dr. Young said.

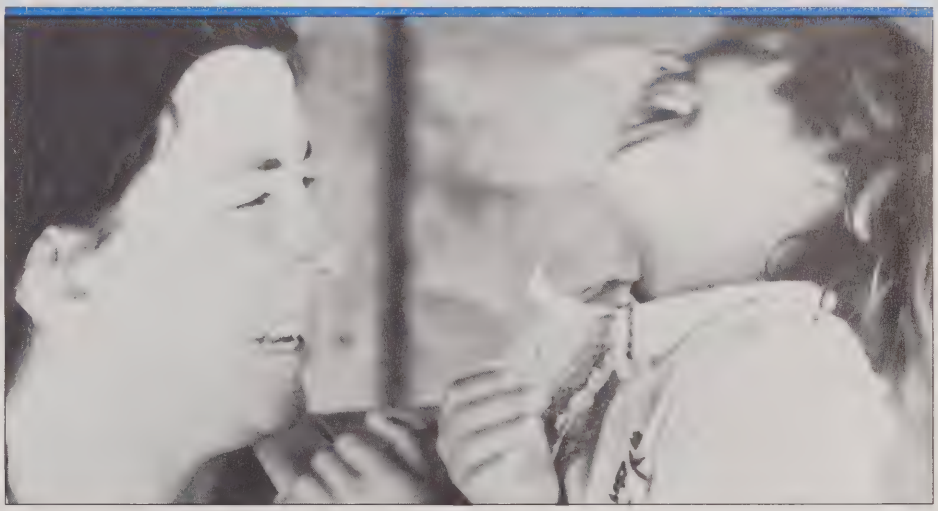
"If I can help them collaborate as well as develop programs that bring the basic science to the clinic as quickly and efficiently as possible and vice versa — that interaction that I've always been so excited about in neurology — if I can facilitate those interactions and make the MGH the place where everybody would send their relatives, that would be great."

As the first woman Chief of Service at the MGH, Dr. Young realizes that she is being watched carefully. "I have to behave myself," she joked.

"I know that neurology is a rather male-dominated specialty, but that never bothered me. I always just felt as though I was doing what I was interested in. Fortunately the people I trained with and worked with always encouraged that interest.

"If I have any impact at the MGH, I hope it is as a role model for how you train young people to be good and self-assured neurologists and scientists who will go out and do what they want to do and what they need to do irrespective of their sex, race, or background.

"If I could accomplish that, now THAT would be wonderful." ■



*"Huntington's patients are some of my favorites," says newly appointed MGH Chief of Neurology Dr. Anne B. Young, shown above with one of the children from the Venezuelan Project. "For the genetic studies in Venezuela we took blood from children as young as four. They behaved like little soldiers, coming in with their arms outstretched, and didn't scream or cry."*

# *Turning 65: The ABC's of Getting Your ZZZZ's*

FEW THINGS in life are as satisfying as a good night's sleep. And few things are as frustrating as being unable to fall asleep.

Among the 29 million Americans now over age 65, more than half experience insomnia or some other sleep problem.

Although sleep patterns change as a person ages, troubled sleep is not necessarily a normal part of aging. An older person does not have to take a sleep disturbance lying down. Often a problem can be remedied with a good medical evaluation and a little common sense.

A normal sleep cycle consists of two different stages — REM ("rapid eye movement" or dreaming sleep) and non-REM (deep sleep). Although the amount of sleep each person needs varies widely, the majority of healthy adults need between 6-1/2 hours and 8-1/2 hours sleep each night. During that time a person will experience 4 to 5 cycles of REM and non-REM sleep.

As a person ages, the hours of nighttime sleep and the amount of time spent in the deepest stages of non-REM sleep decrease.

"Older folks tend to take more of a siesta approach to sleeping," said Dr. John W. Stakes, Director of the MGH All Night Sleep Laboratory. "They typically sleep less at night and nap during the day."

Among the elderly, insomnia is the most common complaint. "They either can't fall asleep or fall asleep too early in the evening, then wake up in the middle of the night and can't fall back to sleep," Dr. Stakes said. "Insomnia is of great concern to older people because they worry that they are jeopardizing their health if they can't sleep continuously through the night. This worry about falling asleep and maintaining sleep only tends to compound the problem."

Insomnia in the elderly is often accompanied by other complaints of sleep disturbances. Sometimes the awakenings are caused by nocturnal myoclonus (unusual leg movements). "Many people throughout life will have occasional leg cramps at night, and these will increase in prevalence in later years," Dr. Stakes said. "There is also a group of patients who have restless feelings and periodic movements of their legs during sleep — kicking or jerking. This can be very distressing and fragment sleep and lead to many disagreeable comments from the bed partner."

The cause of these leg movements is not known but they often increase during the sixth, seventh, and eighth decades of life.

*(Concluded on Page 8)*

## — Getting Your ZZZ's

*(Concluded from Page 7)*

Medication can sometimes bring relief. Exercise may also help alleviate mild cases.

Insomnia associated with breathing problems is less common among the elderly. Sleep apnea (pauses in breathing coupled with loud snoring) occurs in a minority of patients. More common are disruptions in sleep patterns caused by medications or an accompanying medical problem such as arthritis or Parkinson's disease.

"Many medical problems may be well-treated during the day but then get a little out of control at night when medications wear off," said Dr. Stakes. "Many doctors manage a patient's pain and other medical problems very well during the daytime hours but may not attend as well to the nighttime hours."

Obtaining a complete patient history is extremely important in trying to assess the underlying causes of any sleep disturbance.

This history should include a physical evaluation — other ailments and medications, including nicotine, caffeine, and alcohol use — as well as a psychological and emotional assessment of the patient.

Recent changes in lifestyle — retirement, deaths or illnesses in the family, financial pressures, the loss of a pet — are all important factors in a patient's medical history. Alleviating or aggravating factors are also important. Does the person sleep better or worse on a trip? After physical exercise? After eating?

In treating a sleep disturbance, physically addicting sedative hypnotic medications should be avoided if at all possible. "For those people who can't sleep because they're undergoing surgery the next day or facing the loss of a loved one, a brief course of sedative hypnotics may be used," Dr. Stakes said. "But their use should be brief."

Over-the-counter medications are safe although many people develop a psychological dependence on them. "But then many people develop a psychological dependence on an aspirin before they go to bed," Dr. Stakes said. "The aspirin initially may have helped a painful disorder, and then become a habit and thus linked to a good night's sleep."

Many cases of insomnia and troubled sleep can be helped by practicing good sleep hygiene.

To get a good night's sleep:

- Avoid daytime napping.
- Maintain a regular schedule. Fix your hours of wakefulness Monday through Sunday.
- Develop a bedtime routine. Do things each night that give your body and your mind time to wind down.
- Use your bedroom only for sleeping. Do not read in bed or watch television in bed. After you turn out the light, give yourself about 15 minutes to feel drowsy. If you are still awake, get up, and go into another room until you feel drowsy again.
- Avoid stimulants like nicotine and caffeinated beverages, including soft drinks late in the day.
- Avoid alcohol late in the day as well. Even though alcohol is a sedative and may put you to sleep faster, it tends to lighten the sleep stages thereafter. Alcohol can cause a much more restless night than if you had allowed sleep to come naturally.
- For some people a light snack before bedtime can help bring sleep. Others, however, will have nocturnal regurgitation of food and fluid, or experience heartburn, and should avoid eating before bedtime.
- Try to exercise at regular times each day. Moderate physical activity 2 to 4 hours before bedtime may improve your sleep. But heavy cardiovascular exercise (like jogging) too close to bedtime is likely to keep you awake.
- Above all, don't *worry* about trying to fall asleep. "Sleep is one of the body's normal functions," said Dr. Stakes, who is also an Instructor of Neurology at Harvard Medical School. "You can't force sleep upon yourself. It just doesn't work." ■

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MGH News

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*Coming to a Doctor's Office Near You:*

# Videos That Help the Patient Decide on Treatment

A 72-year-old man, married and sexually active, has been experiencing increasingly severe symptoms of bladder irritation and urinary obstruction. The problem is caused by pressure from an enlarged prostate — a male organ that encircles the urethra that carries urine from the bladder through the penis and eventually out of the body.

The man gets up twice a night to urinate and during the day urinates frequently, often feeling a sense of urgency. The man describes his symptoms to his doctor who refers him to a urologist.

The urologist may advise surgery. Surgery involves snipping away part of the prostate and usually relieves the symptoms. In some cases, however, surgery can worsen the symptoms. It also presents risks of complications that can cause incontinence, impotence, or rarely, even death.

The alternative is to live with the symptoms. They may stabilize over time and become less bothersome on their own. In other cases, however, the symptoms may become worse, and the risks of surgery increase when the patient is older and has developed other medical problems.

Neither choice is right or wrong. The decision requires a careful balancing of risks and benefits. The balance may be tilted by the probabilities of good and bad outcomes or by how one would feel about those outcomes if they occurred. When a patient seeks professional advice in a situation like this, it is not uncommon for different doctors to make different recommendations.

"When doctors offer conflicting advice it may be because they have different beliefs about how likely it is that a patient will have a good or bad outcome. Or it may be that the doctors feel differently about the relative goodness or badness of outcomes. For example, 'How does impaired urinary function compare to impaired sexual function?'" said Albert G. Mulley, MD, Chief of the MGH General Internal Medicine Unit. "It can be a difficult, time-consuming process for the patient to learn enough about treatment options to make an informed choice, or for the doctor to learn enough about the patient's preferences to

*(Continued on Page 2)*

*Dr. Valentin Fuster*

## *Valentin Fuster Named New Cardiac Chief*

IN 1914 when Paul Dudley White, MD, the founder of the MGH Cardiac Unit, decided to specialize in cardiology, his colleagues scoffed at the idea.

"Better pick another field, Paul," Dr. White's medical school classmates told him. "Everybody knows there's no future in cardiology."

Today everybody knows Dr. White's classmates were wrong. In this country alone more than 68 million people suffer from some form of heart disease. Nearly half of all deaths each year are heart related.

Fortunately Dr. White did not listen to his colleagues. In 1914, he set up a primitive electrocardiograph machine in a closet at the MGH. Neither the machine nor the building exists today. But that event, as much as any other, marked the birth of cardiology in America.

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INSIDE

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EDITORIAL

# Rating Hospital Specialties

A POLL OF SPECIALISTS has come up with an interesting list of hospitals with highly rated specialties. A University of Chicago agency asked specialists in 15 fields to name the leading institutions in each of the respective fields. From the total votes, about eight hospital departments were chosen as leaders for each field. Massachusetts General Hospital finished first in the country in both cardiology and neurology.

In four other specialties the MGH finished second among the 6,700 hospitals in the United States: orthopedics, psychiatry, endocrinology (hormonal disorders like diabetes and thyroid disease), and gastroenterology (GI). Other highly rated MGH specialties are rheumatology (arthritic disorders), third in the nation; AIDS, fifth; and gynecology, eighth.

There were at least two pleasant surprises in the poll carried out for *U.S. News and World Report*. Psychiatry has traditionally been a very strong field at the MGH, but there are several well-known psychiatric specialty hospitals nationally. The only one that finished ahead of the MGH, however, was McLean Hospital in Belmont, Mass., a sister institution cofounded with the MGH on the same day in 1811. Their first and second finish in the United States was striking.

The other surprise was in one sense even greater. In recent years gynecology at the MGH's Vincent Memorial Hospital division has been a little below its traditional solid capability. With a new service chief who has recruited outstanding gynecologists over the last three years, the MGH department itself has again become outstanding. And its home in the MGH's newly opened Ellison Building has provided the technological efficiency to complement the leading gynecologists. Within the MGH the revolutionary improvement has been palpable and soaring. That the ascendency is already being recognized nationally bodes well for the continuingly improving specialty.

## — *Videos*

*(Continued from Page 1)*

make a recommendation that is consistent with what the patient wants."

What the patient wants.

It sounds like the title of a new hit movie. And in some ways it is.

A unique set of interactive videos designed to help physicians give patients the kind of information that is important to them could be coming to a doctor's office near you as early as next year.

The videos are the products of the Foundation for Informed Medical Decision Making, a nonprofit group founded by Dr. Mulley and several colleagues including John E. Wennberg, MD, Director of the Center for Evaluative Clinical Sciences at Dartmouth Medical School in Hanover, NH.

Not only will the videos facilitate communication between doctors and patients, said Dr. Mulley, but by making patients better-informed, they will also lead to a better-run and more efficient health care system.

"One of the things we haven't done very well historically in medicine is focus on outcomes that are important to patients," Dr. Mulley said. "We've done a very good job of identifying objective outcomes. These are easy to measure; people don't argue about them. So we focus on test results that produce a number like the ejection fraction — how much of the blood in the heart is pumped out with each beat.

"But a person with heart disease doesn't care about the ejection fraction. A person

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with heart disease cares about whether he'll be able to carry a bag of groceries up the stairs without feeling pain, without getting short of breath. In cancer we focus on five-year survival rates. But what may be more important to the patient is the quality of the first year."

Using interactive video technology, Dr. Mulley and his colleagues are taking objective outcomes like five-year survival rates, putting faces on them, and then inviting patients to live vicariously with those outcomes for a few minutes.

In the prostate video, for example, patients describe how surgery has affected their sexual function.

"I was stunned," one man says, describing in detail for the viewer retrograde ejaculation — a backflow of semen into the bladder. At least 65 percent of men who undergo prostate surgery experience retrograde ejaculation. About five percent become impotent.

"We've found that men have very different priorities," Dr. Mulley said. "For one 72-year-old, loss of sexual function may be a very big problem, while for another it may not be an issue. We want to help patients make a choice based on an understanding of the trade-offs. They are the ones whose lives will be affected by the good and bad outcomes."

Interactive video technology allows patients to understand and make those kinds of individual choices. Based on symptom level, age, and other characteristics, an individual patient can be matched with one of 64 possible programs on the prostate video.

"So what the patient gets is information that is quite precisely tailored to his circumstances," Dr. Mulley said. "It's something his doctor, no matter how expert, couldn't do without the help of the computer that drives the interactive video."

Eighty-nine percent of the more than 700 men who have used the video said it helped them make a decision and thought that all men contemplating prostate surgery should see it. In 1990 the video won the gold medal for public education at the 32nd New York International Film and TV Festival.

The prostate video is the first of about 30 such programs the Foundation has planned. Prostate will be the first of four or five on men's urological issues.

Other clusters will include women's health issues (breast cancer, hysterectomy, contraception, infertility, estrogen replacement, etc.); cardiovascular diseases including hypertension, hypercholesterolemia, and angina; bone and joint diseases including back pain, osteoarthritis of the knee and hip, and rheumatoid arthritis.

By next year four videos should be in circulation: prostate, back pain, breast cancer, and hypertension.

"We won't have one for every disease, but by carefully choosing 30 or so, we will cover a lot of the large-volume conditions that often pose difficult choices and/or involve high-cost procedures," Dr. Mulley said.

The idea for the videos came out of the merging of two parallel tracks at the MGH and Dartmouth.

Dr. Mulley and Michael Barry, MD, also a general internist at the MGH, joined an extensive collaborative effort with Dr. Wennberg at Dartmouth to study outcomes of men with prostate disease.

The prostate video was produced on a shoestring with pilot funding from the John A. Hartford Foundation, Inc. of New York. Dr. Barry was largely responsible for the information content and colleagues at Dartmouth provided technical and production skills. Since then the collaboration has become more sophisticated and now includes leaders in the field of medical interactive video technology and medical journalism. The Hartford Foundation continues to support the work and has been joined by the Commonwealth Fund and the Pew Charitable Trusts. The new federal Agency for Health Care Policy and Research has supported some of the research which assures that the video disc programs contain the best available information.

An important objective of the project is to improve the information available to doctors and patients in the future. In light of this, Dr. Mulley is concerned about the trend among insurers to create "practice guidelines" — rules that could be used to govern strictly which patients should receive which treatments.

"Such a system means you're going to be withholding treatments from people who would choose them but also giving those same treatments to other people who would not.

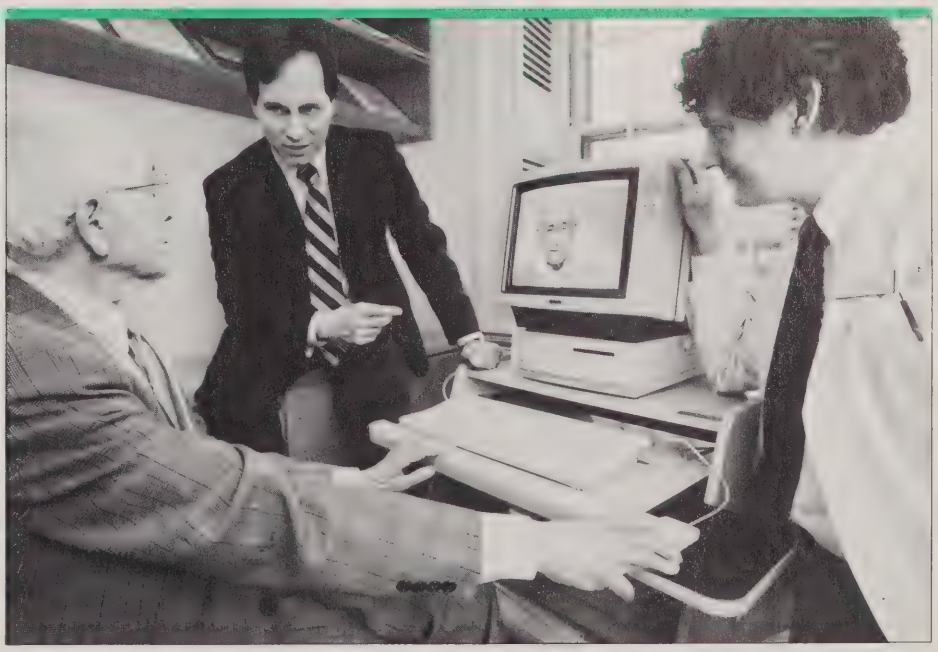
"It just seems ironic that we would allow people to buy whatever kind of car they want, whatever color, whatever size, but when it comes to the most personal goals in life that relate to health care, we would enforce some sort of societal average or group norm."

But Dr. Mulley says the other policy response to rising health care cost —promotion of competition among providers — is equally bad and has also led to inefficiencies by producing duplication of available services and legitimizing induced demand.

"Uncovering the true demand for health care would undoubtedly roll back utilization rates for many costly procedures," said Dr. Mulley, who is also Associate Professor of Medicine and Health Policy at Harvard Medical School.

Maybe yes, maybe no. But at least patients would be more likely to get what they want and not get what they do not want.

"I should have given this more consideration," says one man in the prostate video who elected to have surgery and then experienced several bad outcomes. "I just didn't know. I thought surgery was like getting a haircut. I just wish I had known more about what to expect." ■



*Dr. Albert G. Mulley (center) views a videotape with a patient (left) and Dr. Michael Barry. The video program provides information designed to help the patient make up his mind about different treatment options.*

# Animal Research at the MGH: Tough Standards, Tougher Reviews

ONE OF THE major stumbling blocks in the fight against cancer is the lack of specificity of cancer therapies.

Drugs that kill cancer cells also kill other cells and must be given in such high doses they make the patient sick. The same is true of radiation therapy.

"There are no agents that would go and just recognize cancer cells exclusively," said Tayyaba Hasan, PhD, Team Leader of the Photochemical Targeting Group in the Wellman Laboratory for Photomedicine.

That is why the experiments on a laser-induced ovarian cancer therapy led by Dr. Hasan and her team in collaboration with the Department of Gynecology look so promising at this very early stage.

The approach that these investigators are taking involves the use of special immune system substances called monoclonal antibodies (Mabs) and dyes. Mabs specifically recognize molecules on cancer cells. They are bound with a large number of dye molecules. The idea is to inject the dye-bound Mabs into the body and then shine laser light through optical fibers in the area of tumor tissue where the antibodies have congregated.

The energy from the laser is absorbed by the dye molecules. In this highly active, energized state, the dye molecules are capable of being poisonous themselves or creating other poisonous molecules that kill the surrounding tumor cells.

So far the approach has been successful through several different types of laboratory experiments in cell culture.

The last experiment was the most exciting of all. Researchers took human cells of ovarian and other cancers from the operating room and mixed them with the dye-treated antibodies in a Petri dish (a shallow, transparent dish with an overhanging cover).

"The laser light killed all the ovarian cancer cells," Dr. Hasan said. "But those non-ovarian cancer cells which did not express the molecule that the antibody recognizes, survived."

Even after these encouraging results with human cancer cells, however, Dr. Hasan says the promising new treatment is far from ready for patient use, and in fact may never be translatable to humans.

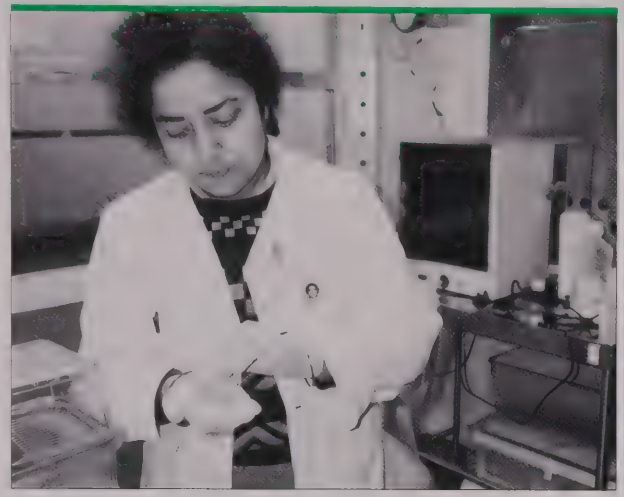
"It would be very exciting if one could go to the patient at this stage, but it's just not a fair comparison," she said. "When you treat your cells *ex vivo* [outside the animal], all the antibody and the dye see are those target cells, whereas *in vivo* [inside the animal] they are going to compete with all the other organs. So far every experiment we've done has been either noncompetitive or wimpishly competitive."

To beef up the competition and make the experiment more true-to-life, Dr. Hasan submitted a request to the Protocol Review Group, a division of the Subcommittee on Research Animal Care, to try the experiment in laboratory mice.

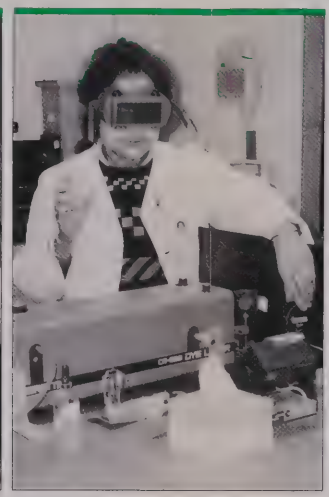
In a living animal, explained Dr. Hasan, many of the Mabs that recognize the ovarian cancer cells are taken up by the liver and the spleen and may recognize other tissue as well. Too much or too long an exposure to the laser could not only kill the cancer cells but might kill the animal as well.

In a living animal in which the disease is progressing and spreading, the optimal time of treatment can be determined, and survival rates and disease recurrence can be assessed. "There are just so many questions that cannot be answered in a Petri dish," Dr. Hasan said. "At some point you have to move to a living, breathing animal."

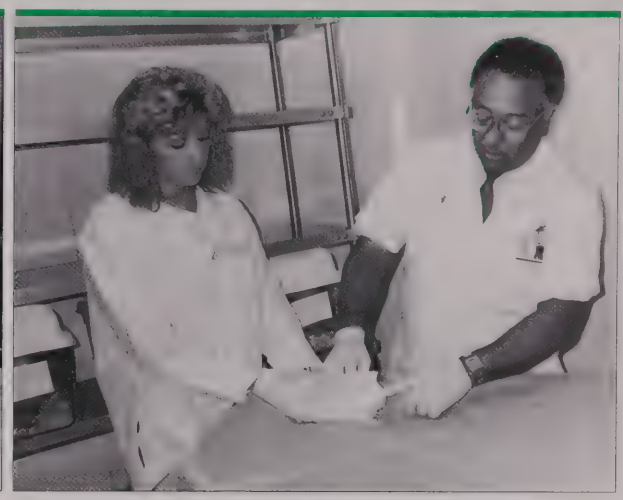
Dr. Hasan received committee approval to use 300 laboratory mice. Not every animal research project at the MGH fares so well. About three-fifths of all animal studies are either deferred or provisionally approved because of questions about protocol.



*Dr. Tayyaba Hasan holds one of the laboratory mice used in experiments on a new laser-induced ovarian cancer therapy.*



*Dr. Hasan examines the argon dye laser used in animal experiments for a new laser-induced ovarian cancer therapy.*



*Dr. William Watson, the hospital's chief veterinarian, and Karen Meeker, an MGH veterinary technologist, conduct a routine examination of one of the hospital's guinea pigs for signs of disease or distress.*

"Our function is really twofold," said Richard D. Granstein, MD, Protocol Review Group Chairman. "First we want to make sure the animals are treated properly and humanely, and second, we want to make sure the research is worth doing. Even *though it's not our task to look at the science per se, we don't want to waste or sacrifice an animal life for something that is not worthwhile even if the animal is treated humanely.*"

Such rigorous oversight of animal research activities at the MGH dates back nearly 30 years. One of the first subcommittees established by the hospital's Committee on Research (set up shortly after World War II) was the Subcommittee on Research Animal Care.

At first the subcommittee primarily concerned itself with the proper housing and care of research animals. During the 1970s, however, as public awareness of animal rights increased, committee members began examining research protocols as well, even though such reviews were not mandated by the federal government until 1985.

"We strongly believe that animal research is necessary, and from the beginning the hospital's position was that we would do it properly," said William Watson, DVM, Director of the Office of Laboratory Animal Resources and the hospital's first fulltime veterinarian.

Members of the committee, who include two community representatives, meet once a month and review all new and continuing protocols (a total of about 800 a year). No protocol has ever been approved without the support of the two community representatives.

"We really view the whole committee as representing animal welfare, but the community representatives who have no scientific background bring a different perspective to the discussions," said Rosalyn A. Gray, Protocol Review Group Manager. "That's why we so respect their opinions."

Aside from reviewing every animal research study at the hospital, the Protocol Review Group also ensures that all state, federal, and local regulations concerning animal welfare are strictly enforced. These guidelines regulate everything from housing and feeding of the animals to their "psychological well-being."

"Psychological well-being hasn't been well-defined," Dr. Watson said. "Basically the U.S. Department of Agriculture has taken a performance-based approach to compliance. They look at the individual animals and determine at that point if they are in a state of well-being."

*At the MGH the three fulltime veterinarians and 23 fulltime animal caretakers ensure that the animals' psychological well-being is maintained with regular exercise for the dogs, special toys, and TV and radio for the nonhuman primates.*

In addition to the mountain of federal and state guidelines governing animal care, the MGH has standards of its own for the care and use of the more than 23,000 animals (predominantly rodents) housed at the hospital.

Only certain rooms, for example, can be used for surgical procedures on animals.

"Sometimes investigators don't agree with this provision," Dr. Granstein said. "It's inconvenient for them. But that's the way it is. The *federal guidelines go only so far. Ours go a little bit farther.*"

In the coming decade Ronald Lamont-Havers, MD, Chairman of the MGH Subcommittee on Research Animal Care and former Director of Research Affairs, believes regulations governing research animals will continue to be strengthened. "I anticipate that by the end of the decade certification will be required of individuals before they'll be allowed to use animals in research."

The MGH is already moving in this direction with a number of educational courses on the proper use and treatment of research animals. "At the moment the courses are voluntary," Dr. Lamont-Havers said. "But I think they will become mandatory before too long."

Although the MGH has more than doubled the size of its research facilities in the last five years, the number of animals used per investigator continues to decline.

Cost is one reason. Rigorous protocol reviews are another. "One trend the committee has encouraged is the shared use of animals whenever possible," Dr. Granstein said. "Someone might need a liver for something; someone else might need a kidney; someone else might need skin. Rather than each of these three investigators ordering separate animals, you could use a third of the animals if they all utilized organs from the same animal or perhaps from an animal that had been sacrificed for a fourth experiment involving something else.

"As much as possible we try to minimize the number of animals used."

Computer modeling, tissue cultures, and other laboratory experiments have also cut down on the use of animals in research. But computers and other substitutes will never totally replace animals in the laboratory.

"Computers can take you a long way," Dr. Granstein said. "But in the final analysis a computer is only as good as the information that's put into it. And the only way you can get that information is from a living animal." ■

## — Dr. Fuster

*(Continued from Page 1)*

Today the MGH Cardiac Unit is internationally renowned. And the fledgling specialty of cardiology that Dr. White helped pioneer has evolved faster and more successfully than probably even Dr. White could have imagined.

*"What is so exciting about this specialty, in my own view, is that the toughest part of cardiology has already been significantly solved," said Valentin Fuster, MD, the newly appointed Chief of the MGH Cardiac Unit and heir to Dr. White's legacy.*

"Today you can approach almost any cardiac disease with positive expectations. There are few conditions that we cannot cure or at least improve through medical or surgical therapy. This provides great satisfaction for somebody in this specialty.

"The next step — and it is a very big step — is to develop a better understanding of the basic mechanism of disease so that we may take appropriate steps toward the prevention of cardiovascular disease in the elderly."

Dr. Fuster, *only the fourth chief in the 77-year history of the MGH Cardiac Unit*, is well-suited to lead the field into the next century.

A native of Barcelona, Spain, Dr. Fuster comes to the MGH from Mt. Sinai Medical Center in New York City where he was Chief of the Division of Cardiology from 1982 until his arrival at the MGH on July 1. From 1975 until 1982 he was a Consultant in Internal Medicine and Cardiovascular Diseases at the Mayo Clinic in Rochester, MN. Before that he spent three years in Great Britain, mostly at the University of Edinburgh in Scotland. He received his medical degree from Barcelona University. It was at Barcelona that Dr. Fuster first resolved to specialize in cardiology.

"I had a good friend I used to play tennis with who had a heart attack at age 35," Dr. Fuster said. "He was a professor of medicine at Barcelona, and he always said to me his weakness in medicine was cardiology. I think he transmitted that sentiment to me so that his weakness would become my strength."

If Barcelona set his direction, the three years he spent training in London and Scotland set his style.

"Those years had a very great influence on me," Dr. Fuster said. "The British system relies heavily on common sense. They take a very pragmatic approach to medicine. The cardiologists there showed me how to arrive at a conclusion by just listening and talking to the patient and relying less on technology and more on physiology."

*"What is so exciting about this specialty, in my own view, is that the toughest part of cardiology has already been significantly solved. Today you can approach almost any cardiac disease with positive expectations. There are few conditions that we cannot cure or at least improve through medical or surgical therapy. This provides great satisfaction for somebody in this specialty."*

— Dr. Valentin Fuster
Chief, MGH Cardiac Unit

Dr. Fuster's experiences in Edinburgh had a profound impact on him. His consideration and devotion to his patients is well-known. *He often describes the time he spends with a patient as "the best time I can spend."*

*"By simply examining and talking to the patient, one can probably get as much as 90 percent of what is needed to make a reasonably accurate diagnosis," Dr. Fuster said. "To me, this is what is so fundamentally enjoyable about this field."*

Much has been made of Dr. Fuster's charisma. Deservedly so. Loyalty among his patients is legendary. Before he even arrived at the MGH, Dr. Fuster's calendar was filled with some of the 400 or more of his patients, including the Secretary General of the United Nations, Javier Perez de Cuellar of Peru, who are following him here.

Dr. Fuster has also inspired great loyalty among his staff.

"He's a very caring person," said Doris Mansfield, Dr. Fuster's Executive Secretary. "He really and truly loves people.

"I remember sitting across the desk from him about two weeks after I started working for him. He was writing. His head was down, and he was very busy. All of a sudden he stopped what he was doing, looked up at me, and said, 'So how are you?'

"I was shocked. He didn't mean, 'How are ya?' the way people ask today. He really meant, "How *are* you?'

"That was my first glimpse into the man's humanness. Since then I've had many more."

Ms. Mansfield and Melissa Curwin, Cardiac Administrator, have both relocated with Dr. Fuster to the MGH. Two senior investigators — Juan Jose Badimon, PhD, and his sister Lina Badimon, PhD — have also followed Dr. Fuster to the MGH.

In the laboratory Dr. Fuster is primarily interested in how coronary artery disease develops. His particular focus is atherosclerotic plaques.

Atherosclerosis is a common condition in which the inside wall of the coronary arteries becomes thickened and clogged with lipids (fat or cholesterol). By narrowing the blood's passageway, these atherosclerotic plaques build up and can lead to strokes and heart attacks.

"Our idea is to try to remove the fat from the atherosclerotic plaque because we feel that the presence of fat there is like a weapon that causes the plaques to rupture," Dr. Fuster said. "And when they rupture, a blood clot forms.

*"So our approach is to begin to look at the possibilities of removing the fat by pharmacological means [using drugs]. We are doing this in the animal model, for example, by injecting high density lipoproteins [HDL, or so-called 'good cholesterol'] into rats. And since we are succeeding in removing the fat in the rat model, now we are moving into the pig model."*

*A second research interest of Dr. Fuster and his colleagues involves finding ways to prevent the process of accelerated coronary artery disease in heart transplantation patients. At the MGH he will be able to see this process first hand in the growing MGH heart transplant program.*

*"This is a major problem today, and I think we have the tools in the animal models and the technology to address this issue vigorously over the next 2 to 3 years," Dr. Fuster said.*

*Vigor is an oft-used word in Dr. Fuster's vocabulary, whether he is speaking English, Spanish, Italian, or French. And it takes vigor — and three separate secretarial shifts — to keep pace with his 16-hour days.* An athletic man whose idea of a vacation is a bicycle tour of Europe, Dr. Fuster is also an excellent tennis player. (Before going into medicine he toyed with the idea of becoming a professional tennis player.)

A prolific writer as well, who has written more than 400 scientific papers, Dr. Fuster brings an irresistible energy level and enthusiasm to the MGH Cardiac Unit.

Dr. Fuster, who has been appointed Professor of Medicine at Harvard Medical School, also has strong opinions about teaching. Many of these ideas are rooted in his own experiences and career.

*"One of my concerns today about the training of young people in cardiology is that it is too technologically oriented," Dr. Fuster said. "The time in which these young people have to be trained is short. At the earliest stages of a young doctor's training, we have to do a better job of teaching him to relate to the patient better, to examine the patient properly without using any technology. Technology is very important, but only as a supplemental tool to increase accuracy."*

Dr. Fuster, a great admirer of Dr. Paul Dudley White, acknowledges that the revolution in cardiology at the MGH has already taken place. "I didn't come here to revolutionize this place," he said. "This place doesn't need much revolution.

"The main goal that I have is to try to integrate the talents that are already here. The Cardiac Unit has excellent clinicians, excellent researchers, excellent patient care. My hope is that I can make this an exciting and pleasant and happy place to work for young people, as well as for seasoned cardiologists." ■

## MGH Rated Best in the Nation

The MGH Cardiac Unit was for the second year in a row named the best in the country in a poll of cardiologists.

A professional polling firm was retained by *U.S. News and World Report* to conduct the nation's third largest newsweekly's second annual poll on medical specialties.

The 280-member Cardiac Unit, which includes 59 cardiac fellows, 55 senior staff, and 166 support staff, is regarded as superb and has been led recently by Roman W. DeSanctis, MD, an internationally renowned cardiologist, as Acting Chief. In the 77-year history of the unit there have been only four chiefs. Founder Paul Dudley White, MD, headed the department for 34 years, followed by Edward F. Bland, MD, Edgar Haber, MD, and now, Valentin Fuster, MD. ■

# Whining Children: Dos and Don'ts for Parents

"ARE WE THERE YET?" How often have parents heard that whine from the back seat of the car? Too many times, most parents will respond.

As soon as they begin to talk, children start to whine. Complaining is a normal part of a child's development, say child psychiatrists. It is how children begin to convey emotion through their language.

"One of the things all children do as they begin to communicate emotion, whether it's with their bodies and stamping their feet, or with their language and whining, is to make their parents, whom they want to appreciate their emotions most, feel how bad they feel. To the extent that their parents have gotten that message, the children feel emotionally understood," said Paula K. Rauch, MD, an Assistant in Psychiatry in the MGH Department of Child Psychiatry.

How to acknowledge a whining child's emotional distress while retaining sanity is a problem all parents face. When the whining starts, how should a parent react? Some Dos and Don'ts:

— Keep the child's development level in mind. With a school-age child you can often work with the whining by first acknowledging the feeling underneath it — "I know you're hot and sweaty sitting in this car; I'm hot too" — and then reacting according to the child's capacity — "If I had magic I'd get us out of here, but I don't, so I guess we're just going to have to be miserable together," or "Why don't you tell me about your baseball game this morning?" or "Let's see how many states we can think of." Simply diverting the child's attention often works well.

— Humor. But be careful that your humor does not belittle or make fun of the child.

— Whining characters from children's stories. "Sometimes you can use humor in an anticipatory way," Dr. Rauch said. "If there's a time that usually brings out the whining, you can say, 'Are we going to be Anastasia and Drucilla [Cinderella's whining stepsisters] in the car today? Or can we get through this without bringing out the whining sisters?'"

*(Concluded on Page 8)*

## — Children

*(Concluded from Page 7)*

— Plan ahead. Anticipate the times that usually cause difficulty and have strategies, such as humor or diversions, ready.

— Involve the child in age-appropriate problem solving. "When you whine, you put me in a bad mood too. How can we avoid it?" Be careful, however, to avoid abstract or overly emotional solutions.

— Use rewards, not threats, to change behavior.

— Give the child attainable goals. Pick small bites of time that are particularly problematic — the period before breakfast, when the child first gets home from school, dinnertime, etc. — and then tangibly reward the absence of whining in that time. Pizza on Friday night for a week of whine-free dinners, for example. "Behavioral change works best when you can break it down into discrete bites that the child can succeed at," Dr. Rauch said.

— Praise the child for not whining. "The great thing about going to the beach today was we all played a game in the car and nobody asked, 'Are we there yet?'"

With preschoolers, whining is often not at the top of the list in terms of the big behaviors parents want to concentrate on changing. If the choice is between whining or throwing things, for instance, whining may not seem a bad alternative. This does not mean that whining in a preschooler is any less distressing to a parent, or that nothing can be done about it. Often simply distracting the child will work. Other strategies:

— Plan ahead. Know the times or situations that can cause problems and have strategies ready — a box of animal crackers for the supermarket, books or toys for the car, etc.

— Intervene sooner rather than later.

— Structure problematic times. "I often prescribe what I call a 'Shirley Temple' for mothers and preschoolers when they first get home from work or school," Dr. Rauch said. "This might be juice in a cup with a maraschino cherry for the child and a lemonade or a glass of wine for mom. Everybody sits down to talk and be together for a few minutes, rather than going straight into action."

— Decide ahead of time what items are not negotiable — toothbrushing before bedtime, drinking milk with dinner, crossing the street with an adult, etc. — and be consistent about them. In other areas where a child can safely make decisions, let him decide — the color of his cup, what game to play, what outfit to wear, etc.

— Above all, never name call and do not belittle a child who is whining.

"The most important thing with any child is learning what works and being proactive the next time," Dr. Rauch said. ■

*Dr. Paula Rauch works on a puzzle with her children, Ben (left), 5, and Laura, 2.*

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# THE WAR AGAINST BACTERIA

## Microorganisms:1 Scientists:1

WHAT SCIENTISTS could not do in the laboratory, nature has done on her own — found a way around yet another antibiotic.

Vancomycin, one of the world's most important drugs for the treatment of a wide range of serious infections, appears to be becoming the latest casualty in the war against bacterial resistance.

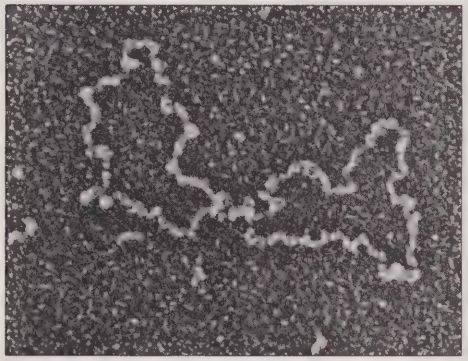
"It seems as though every time we come up with a new drug to fight an infection, the bacteria outsmart us and find a way around it," said George A. Jacoby, MD, a physician in the MGH Infectious Disease Unit.

Sooner or later bacteria develop resistance to just about any antibiotic. Nature's ability to constantly come up with mechanisms of resistance has left scientists both impressed and concerned.

"For awhile we thought vancomycin might be a resistance-free compound," said David Hooper, MD, an Associate Physician in the MGH Infectious Disease Unit. "People tried to make vancomycin resistant bacteria in the lab and failed. But bacteria are very clever. Nature is so flexible and malleable that if you have enough selective pressure long enough you can set up conditions under which resistance may occur."

Resistance has many consequences. In a recent review article for the *New England Journal of Medicine*, Dr. Jacoby wrote that the unrecognized cost of antibiotic resistance in the United States is estimated at

*(Continued on Page 7)*



*A substance called a plasmid, like the one shown above, carries genes for resistance to many antibiotics.*

*Dr. George A. Jacoby studies the transfer of antibiotic resistance between bacteria in his laboratory in Charlestown.*

### The Human Toll Mounts

## *Severe Head Injuries*

EVERY 15 SECONDS someone in the United States suffers a head injury. Every five minutes, one of these people dies and another becomes permanently disabled, according to the National Head Injury Foundation.

Because of its membership in the Boston Med-Flight helicopter ambulance service, its expertise, and its location at the intersection of several major highways, the MGH receives more patients with severe head injuries than many other hospitals in New England.

"We receive an average of two to three head injured patients a day," said Charles J. McCabe, MD, Associate Chief of the MGH Emergency Department. "Eighty percent of the patients we see with serious head injuries have been in a motor vehicle accident. Very often drugs or alcohol are involved."

Nationally half of all severe head injuries are suffered in automobile accidents. The other half, however, happen almost anywhere — in the home, on a bicycle, at work, on a playing field, at the local ice skating rink.

Robert Rafuse, PhD, a 58-year-old electrical engineer and amateur ice dancer, fell skating December 13, 1990. "I got up and drove myself home," Dr. Rafuse said. "I felt fine. I wasn't even dizzy until I arrived home." Six years ago Dr. Rafuse fell ice skating and remained unconscious for three hours. He suffered few ill

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EDITORIAL

# Preventing Head Injury

HEAD INJURIES; The very term induces concern. When a head is traumatized sufficiently to cause brain damage, the stricken person's life is forever changed. Health care offers no second chance as it does, for example, to someone with a limb fracture. At present medical science offers ways to cope with the resultant symptoms but not to repair the damage itself. An article on page 1 poignantly describes the problem. What needs to be revisited, however, is the fact that we as individuals have the knowledge to reduce the risk of head injury and diminish its power to cripple.

The general watchword is "safety." In automobiles we can always wear seatbelts and shoulder harnesses and maintain them in good condition. We can urge further research on treating and preventing head injury and can support legislation to incorporate safety advances into automobiles — even if they impose a financial burden on the consumer. (That cost clearly pales beside the expense of caring for a family member with head injury.) We can obey traffic regulations including speed limits, practice defensive driving, and we can avoid the deadly cocktail of drinking and driving. We can wear helmets when riding bicycles, motorcycles, or similar conveyances, including the again-popular convertible, and require the use of helmets rather than invoking the freedom to avoid them. Society ultimately pays the financial cost of that freedom, anyway, through higher insurance premiums and the dilution of already stretched medical resources.

At home we can adopt a variety of measures: use slip-resistant bathtubs and grab bars, keep bannisters in good repair and stair treads covered by slip-resistance materials, keep floors and stairs free of objects that promote tripping or slipping, avoid overwaxing floors, wipe up spills, light dark areas, etc. Many of these suggestions apply to workplaces as well. In the realm of sports, research has improved and must continue to improve the safety equipment and protective rules of the games.

In summary, as this space has observed before, individuals have the knowledge and power to prevent much illness as well as injury. Therefore we can by employing this knowledge ensure our own and our loved ones improved chances for a healthier life. By so doing we can reduce the need for suffering and the use of high-cost medical technology. ■

## — *Head Injuries*

*(Continued from Page 1)*

effects from that fall.

But after his 1990 fall Dr. Rafuse slipped into a coma for several days. MGH neurosurgeons operated to relieve a blood clot on Dr. Rafuse's brain, but for two months after he regained consciousness, he could not speak, walk, or use his right hand, although he could read. "I could comprehend what people were saying to me but all I could say was 'yes' and 'no,'" he said.

Weeks and months of intensive physical and speech therapy (and later occupational therapy) followed, first at the MGH and then at Spaulding Rehabilitation Hospital, a sister hospital of the MGH.

Although Dr. Rafuse returned to his job at the M.I.T. (Massachusetts Institute of Technology) Lincoln Laboratory in May, he faces many more months of therapy. His speech is still halting, and his syntax out of order. His right arm is still weak but getting better. He walks with a slight limp. He no longer skates and is not yet back to his previous level of productivity at work. But when Dr. Rafuse thinks about where he has been and the potential that lies ahead for his continued recovery, he counts himself among the lucky survivors of serious head trauma. "I'm not one to get frustrated," he said. "I take one day at a time."

The human toll taken by severe head injuries will be the focus this month during

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national observances of Head Injury Awareness Month. It is a toll that affects many beyond simply the injured patient.

About 15 percent of all patients brought to a hospital emergency room with a severe head injury have a life-threatening blood clot. Every second is precious.

"When a patient comes in, the most important task is to get him stabilized and properly ventilated. We then have to determine what other injuries he may have, complete a neurological exam, obtain a CT [computed tomography] scan, and if necessary, get him into the OR as quickly as possible, usually within 20 to 30 minutes," Dr. McCabe said. "The real key is the immediate availability of a neurosurgeon."

The MGH, a Level I Trauma Center, has a neurosurgeon in house and available to the Emergency Department 24 hours a day. The toll on these surgeons can be high.

"The first few minutes after a patient is brought in, your entire physical, mental, and emotional resources are dominated by the technical challenge," said William Butler, MD, an MGH neurosurgical resident. "It's not until you walk into the waiting room and see those anxious faces, the mother crying, the sister with red or blurry eyes, the wife in deep shock, that it hits you that this patient is a human being who loves these people and that these people love him. It's a curious thing. You're not aware of the human element at first. But then when you walk into that waiting room, it hits you hard. Even your voice starts to tremble."

Elaine Woo, MD, Director of the Adult Head Injury Unit at Spaulding and a staff appointee at the MGH, said often equal time and rehabilitation effort must be devoted to the support and training of the family.

"Severe head injury is not a diagnosis of just one individual; it's a diagnosis of an entire support system as well," Dr. Woo said.

For Robert Rafuse, the support system that helped him through his rehabilitation extended beyond his wife Nan Lux and two children and three stepchildren to include other head injured patients. "I encouraged them," he said. "My motto was, 'We Can Do It!'"

Moreover, a serious head injury is devastating not only to patients and their families but also to the caregivers working to put shattered lives back together.

"If we think too closely about what we're doing, it can get very painful for the staff," said Dr. Woo, who is also Chairperson of the Professional Counsel of the Massachusetts Head Injury Association. "It's very important to have a support system for the caregivers as well."

The NHIF estimates survivors of severe head injury face an average 5 to 10 years of intensive medical and rehabilitation services.

"After many moderate to severe injuries, a patient never fully recovers," Dr. Woo said. "All the hopes, the plans, the relationships, the potential — just wiped out. Even so-called 'milder' injuries take their toll on the patient and the support system with persistent physical symptoms and difficulties coping during recovery."

And perhaps it is this sense of irretrievable loss that makes severe head trauma so particularly devastating for all who come in contact with it.

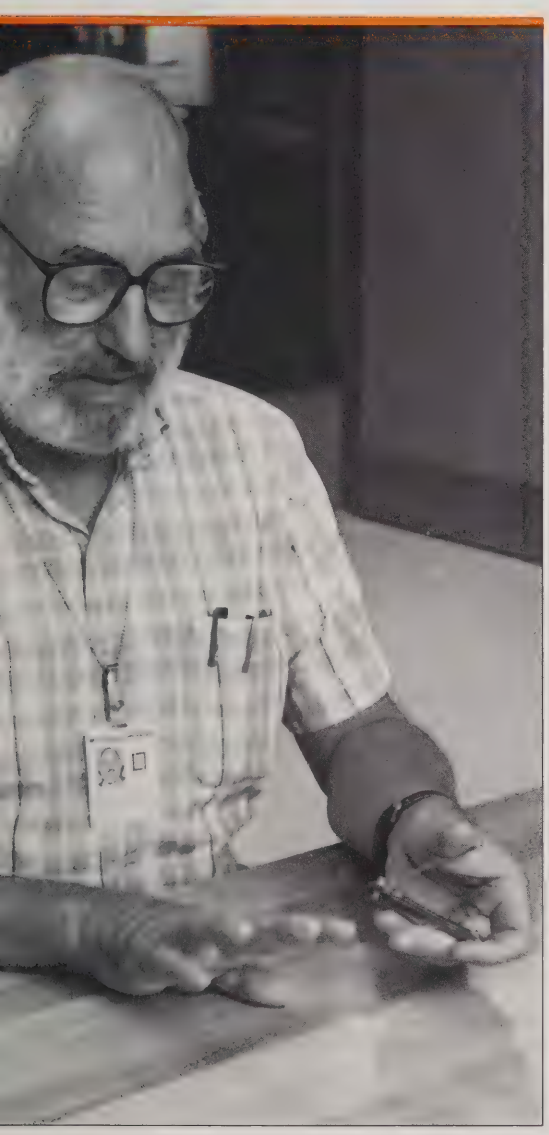
"Once the brain is damaged, it's damaged," said David M. Frim, MD, PhD, an MGH neurosurgical resident. "We can take out the part that's damaged. We can take out a blood clot. But we don't have the medical technology or the ability to be able to put something back into the brain. Once the brain is damaged, all we can do is support what's left."

Researchers, however, continue to work toward the day when they will be able to offer more than simply support but real hope for families and loved ones of severely brain damaged patients.

At the MGH, for instance, Seth P. Finklestein, MD, Director of the Central Nervous System Growth Factor Laboratory, is investigating ways of preventing neurons from dying in stroke and severely brain injured patients, and how to enhance neurological recovery in such patients.

Dr. Finklestein's work, which is being carried out in collaboration with Michael A. Moskowitz, MD, Chief of the MGH Stroke Research Laboratory, has progressed into several animal studies.

"We want to solve the riddle of how recovery occurs in the nervous system," Dr. Finklestein said. "Although brain neurons do not fully regenerate after injury, recovery routinely occurs. We want to find out how this process happens, so we can accelerate it." ■



*Dr. Robert Rafuse, an electrical engineer, suffered a serious head injury last December when he fell ice skating. As an outpatient twice a week at Spaulding Rehabilitation Hospital, Dr. Rafuse continues extensive speech, physical, and occupational therapy. Above, he works with a pair of nail clippers in an effort to regain the use of his right arm.*

## Cardiac Surgery and Neurosurgery

SEPTEMBER'S *MGH News* had a three-paragraph article on MGH Cardiology being chosen number 1 in the country by a national poll of specialists. An editorial mentioned MGH Neurology as also being named the best in the United States.

And so they were. What the brief presentations did not say, however, is that in seeking to rank those fields the specialists included the totality of the care of cardiac disease and the totality of the care of neurological disease. In so embracing the broad view of Cardiology and Neurology, the specialists were therefore really including Cardiac Surgery and Neurosurgery at the MGH as the best in the country.

In fact, it is impossible to have any kind of top-rated specialty without the support of other strong departments such as radiology, anesthesiology, and pathology, for example. This fact is taken for granted by the specialists who voted four other MGH departments as the second best in the nation, and one each as third best, fifth best, and eighth best. ■

# Winds of Change Transforming Psychiatric Care

MORE CHANGE has swept across the rolling lawns and campus of McLean Hospital in Belmont over the last five years than at any other period in the MGH affiliate's 180-year history.

Since the Massachusetts Legislature chartered the MGH and McLean in 1811, McLean, the nation's third oldest psychiatric hospital, spent the better part of its existence treating inpatients.

In recent years, however, changing attitudes toward mental health care as well as changing reimbursement patterns for this care have created dramatic changes at the institution.

Two years ago, the average length of stay at McLean was 71 days. This year the average stay is 41 days and over the last two months it has dropped to 28 days. Over the same two years the number of patients admitted has risen from 1,600 a year to 2,800.

The result of all of these changes has been a decrease in the number of staffed inpatient beds and an equally sharp rise in the number of community residence beds, which allow patients more flexibility to come and go. McLean is still one of the nation's largest private psychiatric hospitals, but it now also runs the largest community residence program as well.

"One has to stop looking at psychiatric care as a series of boxes where you get treated at one hospital, then go to another hospital because it doesn't work out. And then you either stay there until you get better or you get sent somewhere else," said Joseph T. Coyle, MD, Chairman since July 1 of the newly consolidated Harvard Medical School Department of Psychiatry, which includes McLean. "That kind of a system doesn't provide good care. It's inefficient, and being inefficient, it's expensive.

"What's been developed at McLean, and what we want to develop to an even greater extent, are integrated services with graded levels of care that are between outpatient and inpatient. In this way patients can be moved through different levels of care short of hospitalization and often prevent the necessity of hospitalization."

McLean has been a leader in this movement toward a more integrated system of care. The hospital's 127 community residence beds are spread through 10 or more facilities ranging from three-quarterway houses (three-quarters of the way out of the hospital), to halfway and quarterway houses, to community apartments.

In addition McLean's ambulatory care (outpatient) service continues to expand. Last year there were more than 40,000 patient visits at the eight outpatient clinics, said Steven M. Mirin, MD, General Director and Psychiatrist-in-Chief at McLean.

*McLean staff members stop for a few minutes in front of South Belknap, one of the inpatient residences in the Affective Disorders Program.*

Although McLean was cofounded with the MGH, it actually opened three years earlier (in 1818) than the general hospital. First called the Asylum for the Insane, McLean was renamed in 1826 in memory of John McLean, a wealthy Boston merchant who bequeathed the hospital the then-staggering sum of $120,000.

At the time McLean opened, there were few asylums, and conditions for the mentally ill were an abomination. Patients were often housed in jails or poorhouses and were chained, beaten, and starved. The emphasis was on containment and confinement.

From the beginning, McLean emphasized rehabilitation and the restoration of mental health. Over the years the institution has continued to be at the forefront in other areas of the profession as well.

Hand-in-hand with the trend at McLean toward an expanded and more integrated system of care has been the move toward specialization. Three years ago McLean inaugurated a "programmatic" structure of specialized treatment for its patients.

The six programs at the hospital include:

— The Affective Disorders Program which offers specialized treatment for individuals with a variety of problems, including depression, manic depressive disorder, multiple personality, and post-traumatic stress disorder.

— The Psychosocial Program which treats patients whose difficulties require an intensive focus on interpersonal and social functions and on their severe problems of managing feelings and behaviors; patients with personality disorders, eating disorders, obsessive-compulsive disorders, phobias, and chronic pain.

— The Psychotic Disorders Program which treats patients with conditions such as schizophrenia, delusional disorders, psychotic depression, or severe compulsive behaviors.

— The Alcohol and Drug Abuse Program which provides comprehensive diagnostic, treatment, and aftercare services for adults suffering from alcoholism or substance abuse.

— The Geriatric Psychiatry Program which treats older adults suffering from a wide range of psychiatric disorders brought on by chronic medical illnesses or senile dementias.

— The Child and Adolescent Psychiatry Program which offers specialized care in a range of problems affecting this population, including depression, social isolation, and self-destructive behaviors such as suicidal behavior, drug and alcohol abuse, and physical and sexual abuse.

Each program consists of one or more inpatient units, an outpatient component, as well as halfway or community residences.

"Within each program there's the opportunity to provide a continuity of care from inpatient to ambulatory," Dr. Mirin said. "Each program is designed very specifically to meet the needs of the population it serves."

The Psychotic Disorders Program, for instance, has four inpatient units, an outpatient component, and an on-grounds community residence facility and partial hospital program.

The Alcohol and Drug Abuse Program, on the other hand, has a 24-bed inpatient unit, a large outpatient clinic, and an on-grounds community residence.

Dr. Coyle said specialization is a trend not only at McLean but also within psychiatry in general.

"There is a good deal of interest in more clearly defining subspecialties in psychiatry and developing explicit requirements for training programs and certification procedures," said Dr. Coyle, who sits on a Scientific Council of the American Psychiatric Association studying just that issue. "I think we have the opportunity at McLean and some of the other Harvard hospitals of taking the leadership role in developing subspecialization in psychiatry."

*The rolling, secluded lawns of McLean Hospital in Belmont, MA give the MGH affiliate the atmosphere of a college campus. In recent years winds of change blowing across the McLean campus are transforming psychiatric care.*

Another trend in psychiatric care being emphasized at McLean is "case management services." These are services designed to help individuals maintain or regain their independence in society.

"There is a recognition that chronically ill patients particularly need not only psychotherapeutic help but also help in various other ways, such as managing their medications and their finances — negotiating all the many difficulties of daily life," Dr. Mirin said. "So there is much more emphasis on vocational and social rehabilitation."

Part of this trend includes such programs as "after hours" treatment for drug and alcohol patients. Instead of hospitalized care or outpatient sessions during the day, the individual comes for treatment after work and on weekends. Again the emphasis is on keeping the individual functioning in the community.

In these and in many of its other programs, McLean and the MGH are quite complementary. The MGH has strong psychiatric consultation/liaison services, a large ambulatory service, a substantial public sector component at the Lindemann, and a 20-bed inpatient unit.

"There is thus great potential for cross fertilization and collaboration in clinical care, teaching, and research," noted Dr. Mirin.

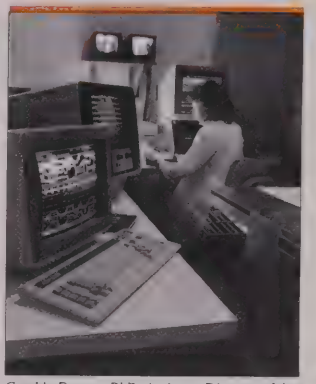
**A University of Chicago-conducted national poll of American psychiatrists recently found McLean and the MGH complementary in another way. Published August 5 in *U.S. News and World Report*, the poll named McLean the best in the United States for psychiatric care. Second in the country for psychiatric care? The MGH.**

Research is also a growing emphasis within psychiatry and especially at McLean, which established the first research laboratories in a psychiatric hospital in the United States 103 years ago.

McLean's $15 million annual research budget is the largest of any private psychiatric hospital in the country. More than $5 million a year is spent on substance abuse and alcoholism research alone. The scope of the hospital's research efforts ranges from basic, fundamental investigations into the workings of the brain and the causes of psychiatric disorders, to patient trials for new drugs and treatments.

Outcome research is also becoming an increasingly important trend in psychiatry. "It's important because more and more we are being called upon to justify and demonstrate that what we do is actually useful to the patient, not only in the short run but also in the long-term," Dr. Mirin said.

"In the Psychotic Disorders Program, for example, we have investigators who are looking at the long-term outcome of people following their first hospitalization for manic depressive and other psychotic disorders. We're looking at what the outcome is of those patients years down the road and trying to ascertain what clinical and social factors contributed to that outcome."



*Cynthia Dorsey, PhD, Assistant Director of the McLean Sleep Disorders Center and Sleep Research Program.*

McLean is also a participant, and Dr. Mirin the principal investigator, in a treatment outcome study funded by the National Association of Private Psychiatric Hospitals.

"I think increasingly we're going to be getting involved in these types of outcome studies," Dr. Mirin said.

Over the next several years Dr. Mirin said McLean will continue to change and expand in the direction of community residence and ambulatory care.

"Ultimately our job will be to keep people out of hospitals living productive lives in the community," he said. ■

# *New Psychiatry Chief Faces Balancing Act*

Joseph T. Coyle, MD, Chairman of the newly consolidated Harvard Medical School Department of Psychiatry, admits he is walking a tightrope in his new position — trying to encourage continued independence at four separate hospitals and integrate them all at the same time.

"Each of the psychiatry departments at these hospitals has its own area or areas of clinical and research strength," said Dr. Coyle, who will lead the psychiatry departments at the Massachusetts General Hospital, McLean Hospital, Massachusetts Mental Health Center, and New England Deaconess Hospital.

"I think it's important to acknowledge these differences among the hospitals and to work to enhance the excellence of each institution consistent with its traditions. At the same time, we want to develop a department with complementary programs rather than competing programs."

Altering the medical school's training program in psychiatry will be one of Dr. Coyle's first efforts in this regard.

"Right now training is balkanized among these different departments," Dr. Coyle said. "I want to look at ways in which we can reduce the number of separate training programs in favor of a more integrated program that allows the residents who come through here to take advantage of the outstanding clinical experiences and faculty scattered at the different hospitals."

Not surprisingly, Dr. Coyle, the Director of the Division of Child Psychiatry at Johns Hopkins University School of Medicine from 1982 until this summer, will concentrate initially on child psychiatry.

"I want to stress the importance of the developmental aspects of psychiatry," Dr. Coyle said. "There are a number of small programs in child psychiatry at the Harvard hospitals. I'd like to tie these all together into one or two programs that have the critical mass of trainees as well as faculty members. I think if we do that, we'll have the best training in child psychiatry in the country."

Similarly, Dr. Coyle pointed to the other end of the age spectrum — the rapidly expanding field of geriatric psychiatry — as another potential area of consolidation.

"Harvard has some outstanding fundamental research going on related to the causes of dementia. There are also a number of outstanding clinicians in geriatric psychiatry at Harvard. Again I would like to do something that would harness those resources to make this a major center for clinical and integrated basic research in geriatric psychiatry."

Dr. Coyle's own research has focused on neurotransmitters, the chemical messengers that neurons in the brain use to communicate with one another.

"Over the years we've been very interested in why neurons die in the brain in conditions such as Huntington's and Alzheimer's diseases, and ultimately lead to the psychopathology [disease process of the mind] of those disorders," Dr. Coyle said.

One neurotransmitter Dr. Coyle and his colleagues have been investigating as a possible culprit in neuron death is composed of glutamic acid. "We think some neurons might die because receptors on them that respond to glutamic acid become overly stimulated."

In laboratory experiments Dr. Coyle has showed that injecting an analogue (chemical equivalent) of glutamic acid into the brain of a rat will produce Huntington's disease in the rat.

"Our most recent work has focused on why neurons die when these receptors are overstimulated," Dr. Coyle said. "It's our belief that if we understand that, then we might be able to develop pharmacologic [drug] strategies to reverse that process and thereby protect individuals who are genetically vulnerable to Huntington's disease from developing the neuronal gap that strikes these patients."

With regard to Alzheimer's disease, Dr. Coyle and his colleagues are investigating genetic similarities between Alzheimer's and Down's syndrome. "We were

"What is the Department of Psychiatry at Harvard? Is it the MGH? Is it McLean? Is it Mass Mental Health? Is it the Deaconess? I think the answer to that question is all of these institutions. Psychiatry at Harvard is a whole group of very excellent clinical experiences, research experiences, and training opportunities that can be melded together into a single, integrated department."

*Dr. Joseph T. Coyle, Chairman of the Department of Psychiatry at Harvard Medical School*

struck by the observation that all individuals with Down's syndrome developed Alzheimer's disease if they lived to midlife," Dr. Coyle said. "This suggested to us that a gene or group of genes located on chromosome 21 [the abnormal chromosome responsible for Down's syndrome] might be involved in the physiology of Alzheimer's disease."

Dr. Coyle and his team are currently exploring this possibility in laboratory mice.

Dr. Coyle said the recent appointments of Anne B. Young, MD, PhD, as Chief of the MGH Neurology Service *(MGH News, June 1991)* and Gerald D. Fischbach, MD, as Director of the MGH Neuroscience Center, contributed to his decision to relocate here. Both Dr. Young and Dr. Fischbach are working on related research. "There are all sorts of very good people at the MGH," said Dr. Coyle, who has also been named Eben S. Draper Professor of Psychiatry at Harvard Medical School. "It's a very good environment."

In fact, strengthening the research ties between psychiatry, medicine, and neurology — a major emphasis already at the MGH — is a goal of Dr. Coyle's for all the Harvard-affiliated hospitals.

But so is nurturing the mental health programs for the poor at Cambridge Hospital (part of the Harvard teaching hospital system), and reinforcing the outstanding alcohol treatment facilities and community residence programs at McLean Hospital.

"What is the Department of Psychiatry at Harvard?" asked Dr. Coyle. "Is it the MGH? Is it McLean? Is it Mass Mental Health? Is it the Deaconess? I think the answer to that question is all of these institutions. Psychiatry at Harvard is a whole group of very excellent clinical experiences, research experiences, and training opportunities that can be melded together into a single, integrated department." ■

# — The War Against Bacteria

*(Continued from Page 1)*

more than $100 million annually. Much of this cost is associated with longer hospital stays for patients infected with drug-resistant organisms.

Scientists also worry that so-called "andromeda" strains of bacteria — organisms so resistant that no drug will work against them — may develop.

"So far that kind of awful bug hasn't happened," Dr. Jacoby said. "There's always been something we could use. But some bugs are getting darn close."

Despite their versatility, bacteria have a limited number of resistance mechanisms. Organisms become resistant in one of three general ways — by making an enzyme (a biological catalyst) that either modifies or destroys the antibiotic, by changing their "targets" — the place where the antibiotic impacts; or by becoming less permeable (penetrable) to the antibiotic. A resistant organism may use more than one of these strategies.

The genes (units of inheritance) that control these mechanisms are often carried on "plasmids" — pieces of excess genetic luggage a bacterium carries around and can either unpack when it needs to or transfer to another organism.

Plasmids vary from a thousandth to a tenth the size of the bacterial chromosome. They can contain as few as 1 or 2 or as many as 500 genes.

"Plasmids have value to the bacteria because they can provide it with extra functions, and yet those functions can be packaged in a very disposable way," Dr. Jacoby said.

Plasmids that carry resistance genes (R-plasmids) provide a bacterium a particularly important survival function.

"I compare it to having a few snow shovels in Dallas," Dr. Jacoby said. "Most of the time the bacteria don't need the R-plasmid because they're not around an antibiotic very often. But just as it can snow even in Texas, the organism may find itself in a hospital in a patient where having the potential to thrive despite being bathed in antibiotics can be very important. And that valuable property can be shared by a plasmid that can spread in a population."

The more scientists learn about bacteria and the mechanisms of resistance, the more impressed they become with their test tube adversaries.

"There is a good deal of concern among medical people that we're seeing both increased resistance among organisms previously susceptible to routine antibiotics and that we're also seeing new mechanisms of resistance," said Mary Jane Ferraro, PhD, Director of the MGH Microbiology Laboratory.

Several recently reported cases of vancomycin resistance underscore the medical community's growing concern about new mechanisms of bacterial resistance.

*Clinical Laboratory Technologist Nancy McCarthy selects bacterial colonies for susceptibility testing.*

Vancomycin, which has been in use since the early 1960s, is an extremely effective treatment against staphylococcal infections. These are a wide variety of serious infections ranging from skin and soft tissue infections to pneumonia and bloodstream infections.

"When penicillin was originally introduced in the 1940s, staphylococcus was 100 percent sensitive to it," Dr. Jacoby said. "But within a decade all over the world the situation had changed because an enzyme that destroyed penicillin had become common in staphylococcus."

At the MGH, for example, nearly 90 percent of all staphylococcal infections are resistant to penicillin. "So a physician would almost never use penicillin to treat one of those infections," Dr. Ferraro said.

To take the place of penicillin, scientists developed methicillin. The staphylococcal bacteria responded to that drug by developing yet another kind of resistance.

"At the MGH about five percent of *Staphylococcus aureus* infections [the most common and important pathogen of the staphylococci] are resistant to methicillin," Dr. Ferraro said. "At other institutions, however, it's a very bad problem — as high as 50 percent or more."

The best antibiotic doctors now have to treat these serious infections is vancomycin. Because of its effectiveness, the frequency of methicillin resistance, and the dramatic rise in cardiac surgery which has greatly increased the numbers of hospitalized patients at risk of developing one of these infections, vancomycin has become one of the most widely prescribed antibiotics at the MGH.

But beginning about two years ago with a report from England, followed by one from France, and more recently, by several in the United States, isolated instances of vancomycin resistance have been docu-

*(Concluded on Page 8)*

## — Bacteria

*(Concluded from Page 7)*

mented. So far this resistance has been found in enterococci, a relative of staphylococci.

"Since these organisms can share plasmids, the concern is that vancomycin resistance will spread to staphylococci and take away one of our very best antibiotics," Dr. Jacoby said.

"This is a totally new phenomenon," added Dr. Ferraro. "Vancomycin resistance didn't exist until only a couple of years ago. Potentially it's a very major problem."

The vancomycin example also illustrates the lag time that may exist in developing bacterial resistance for some drugs but not for others.

"There isn't any way to have predicted — even in retrospect — that penicillin resistance to staphylococcus would appear almost instantly," Dr. Jacoby said. "Vancomycin resistance, in contrast, took 25 years to first crop up."

Vancomycin is only one drug where bacterial resistance is causing concern. Resistance also threatens several other classes of important drugs.

As the search for new and better antibiotics heats up, scientists continue to refine their tools and tactics. The days of the old broad-spectrum, "good-for-what-ails-you" antibiotics are gone. Today, high-tech "designer drugs" modeled on a computer screen are the latest weapon in the war against bacterial resistance.

"There is a realization that antibiotics that would kill a whole spectrum of bacteria is the wrong approach," Dr. Ferraro said. "By affecting microorganisms unnecessarily, they might actually lead to more resistance. The approach now tends to be more targeted."

In the past, researchers developed new antibiotics by screening soil samples for antibiotic-producing microbes. "The difficulty with that approach is that with time the problem of rediscovering already known antibiotics increases," Dr. Hooper said.

Today, molecular biologists have a much better understanding of the targets of antibiotics and of bacterial physiology in general. Armed with this new knowledge, researchers can take a much more precise approach to new drug development.

"By starting from the target and not from a blind search in soil, we may be able to come up with better antibiotics," Dr. Jacoby said.

Computers will play a major role in the development of these new, highly targeted "designer drugs."

"A computer allows you to call up a molecule in all of its three-dimensional glory. You can then look for other agents and chemicals in your vast computer database that might be able to fit into that molecule's target, like a key in a lock, and unlock it," Dr. Jacoby said. "That kind of computer-aided design is just getting off the ground."

The technology of bacterial resistance warfare is impressive. But will it be enough to win the war? Will scientists ever design the perfect antibiotic? — a drug so smart bacteria will never figure it out and overcome it?

"I would say it's very unlikely," said Dr. Jacoby, who is also an Associate Professor of Medicine at Harvard Medical School. "Our experience to date has made us pretty impressed with the bacteria's ability to come up with ways around anything we've been able to throw at them."

In the war against bacterial resistance, staying even may be the best scientists can hope for. ■

*Dr. Mary Jane Ferraro (standing), Director of the MGH Microbiology Laboratory, and Senior Technologist Jacqueline Eversley examine the results of a susceptibility test.*

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MGH News

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*New Group to Treat Workers, Workplaces*

# 'Sick Building Syndrome' A Growing Problem

More Americans die each year from illnesses they catch at work than in motor vehicle accidents.

And more often than not, the diseases come not from a sick colleague but from a sick workplace.

"Sick Building Syndrome" — a building with inadequate ventilation — is just one aspect of the rapidly expanding field of occupational medicine.

Not too many years ago, work-related diseases and injuries were largely considered a problem only for factory workers, miners, construction workers, farmers, and manual laborers. Today occupational illness and disease cut across every job category from bosses to secretaries, from factory workers to office workers.

In 1987, the last year for which figures are available, the Chicago-based National Safe Workplace Institute estimated some 75,000 Americans died from work-related diseases. Another 7,000 to 11,000 died in work-related accidents.

"Occupational disease is one of the great 'unders' of American health care," according to the Institute's 1990 report, *Beyond Neglect: The Problem of Occupational Disease in the U.S.* "It's under-recognized, under-reported, under-studied, and under-prevented."

To underscore this point, a group of MGH specialists have recently joined together to form a new group practice. The focus of the group — Occupational

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A Rash Solution for the Bruins
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*A STAR Is Born*

## High-Tech Marriage Brings Fresh Hope to Brain Tumor Sufferers

A high-tech marriage between "something old" and "something new" has brought increased hope to patients with a wide variety of brain tumors and blood vessel abnormalities.

For years doctors have recognized the inherent advantages of proton beam therapy for the treatment of brain tumors and arteriovenous malformations.

But not until last year were they finally able to fully exploit these advantages through the use of modern-day imaging techniques. The union of the two technologies by MGH scientists has brought fresh hope to patients with these conditions and won national and international awards for design excellence.

Proton beam therapy is a type of radiation therapy known as radiosurgery.

*(Continued on Page 2)*

## 'Homegrown Boy' Named Pathology Chief

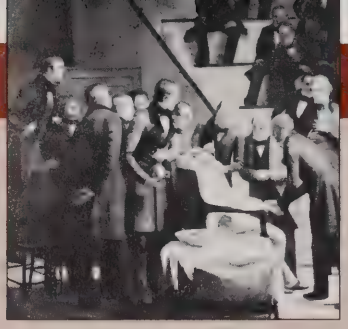
Two weeks after a seemingly routine kidney transplantation the organ began to fail. When the patient failed to respond to conventional remedies, his surgeons knew it was time to call in the cell detectives.

The detectives — medical doctors known as pathologists — recommended the surgeons perform a needle biopsy on the patient.

Using a local anesthetic, the surgeons extracted from the donor kidney a piece of tissue about the size and length of a pencil lead. They then turned this tiny clue over to the pathologists for analysis.

*(Continued on Page 7)*

EDITORIAL



# Science, Errors, And Fraud

WHEN THERE'S INVESTIGATORY WORK to be done, to be done, a researcher's lot is not a happy one. With apologies to Gilbert and Sullivan's "Pirates of Penzance," this paraphrase frequently hits the bulls-eye these days. Especially so when the investigatory work is being scrutinized by the U.S. Congress.

Research machinations are not a recent invention. Someone must have taught the serpent in the Garden of Eden how to fake speech in order to tempt Eve with the apple. With the development of increasingly large research groups, there *is* a danger of less close supervision leading to more abuses. It *is* likely, however, that "research fraud" is already more common today than formerly for at least four reasons: 1. There are far more scientists and studies now (within and without the United States) than ever before. 2. There is more scrutiny of science than ever. 3. The mass media is now more technologically skilled at disseminating information and thrives on negative information. 4. What passes as fraud is often mislabeled.

There can be no doubt that the United States carries out exponentially more research than even a few years ago. As to point 2, most fair people would concede there is a more concerted effort by the federal government and by private individuals to uncover research fraud. So long as the government's process is fair in this pursuit, heightened investigation is a positive. Innocent scientific errors are replete and certainly not confined to 1991. Would it be fair, for example, to dismiss the early Greeks as fraudulent researchers because they assigned lack of motion to Planet Earth and placed it at the center of the solar system? Of course not. Nor were all the clerics who milleniums later perpetuated that misbelief involved in a research fraud coverup. Most people would agree that these were honest errors.

Science moves in fits and starts, and each lurch is not an advance. Often the new direction pointed to is a mistake. That error may be fundamentally wrong as in the tenet that the earth stands still while the other planets and sun circle it in obeisance. Or rather than being an error, a finding may merely be incomplete as in Newton's Law of Gravity. It took until Einstein to expose the oversimplicity of that Law — but it was not oversimplified because of Newtonian fraud, nor does anyone think so.

Scientists do make *honest* mistakes. Indeed given the complexity of this awesome universe, it is man's lot to blunder repeatedly. In blundering, the researcher may lead his colleagues on a false, time-consuming path. When colleagues eventually find their way to the proper trail, the original, unfortunate, scientific wanderer sometimes gets tagged a miscreant who committed fraud.

Most of the time he is embarrassed enough by his mistake without being mortally wounded by suffering the additional opprobrium of false accusation. ■

## — High-Tech Marriage

*(Continued from Page 1)*

Specialists aim high doses of specifically targeted radiation into tumors and other lesions to treat them.

Unlike other types of radiation treatments, however, proton beam therapy is less damaging to normal tissue.

"If you aim a proton beam at something, it will deliver most of its radiation right at the end of its beam path," said Paul H. Chapman, MD, an MGH neurosurgeon. "Other types of radiation deliver their radiation progressively as they pass through the tissue so that the dose is highest where it enters the tissue and then becomes progressively less as it passes through the tissue. This means that normal tissues can potentially receive a fairly high dose of radiation.

"The protons, on the other hand, don't deliver much of their radiation until they get near the end of the beam path and then they deposit it all right at a spot."

That spot is called the "Bragg peak."

Scientists and doctors have known about the Bragg peak and the advantages of proton beam therapy since at least the end of World War II. That is when several proton beam cyclotrons — a device for accelerating particles such as protons — were built. The first of these cyclotrons was built soon after World War II at Berkeley. The second was built at Harvard in 1947-48. The Harvard cyclotron, still in full-time service, is supplying the proton beams used by the MGH physicians.

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William H. Sweet, MD, now a Senior Neurosurgeon at the MGH, quickly recognized the possibilities that the proton beam might offer for treating patients and organized a program to accomplish this. Since that time the MGH and Raymond N. Kjellberg, MD, of the neurosurgical service have gained worldwide prominence for the treatment of brain lesions using the proton beam *(MGH News, June 1979).*

In order to take advantage of the Bragg peak with the proton beam cyclotron, doctors first have to be able to see the target. They then have to be able to position the target in the beam.

The development of three-dimensional imaging techniques such as CT (computed tomography), and more recently, MRI (magnetic resonance imaging), have greatly improved surgeons' ability to see abnormalities within the brain. They have also opened up new possibilities for aiming the beam using the principles of stereotactic surgery.

Stereotaxis (precise positioning in space) is another technology in neurosurgery which has blossomed in the past few years. But adapting modern stereotactic technology to the Bragg Peak — i.e. positioning the patient in space so that the Bragg peak is brought into alignment with the target — proved more difficult.

Until last year.

A three-year project sponsored by Nicholas T. Zervas, MD, Chief of the MGH Neurosurgical Service, included members from the MGH neurosurgery, radiation medicine, and biomedical engineering departments. The MGH team commissioned Product Genesis, Inc., a private product design and engineering firm in Cambridge, Mass., to design and build the first "STAR" unit.

The name is an acronym standing for Stereotactic Alignment for Radiosurgery.

And a "star" it is.

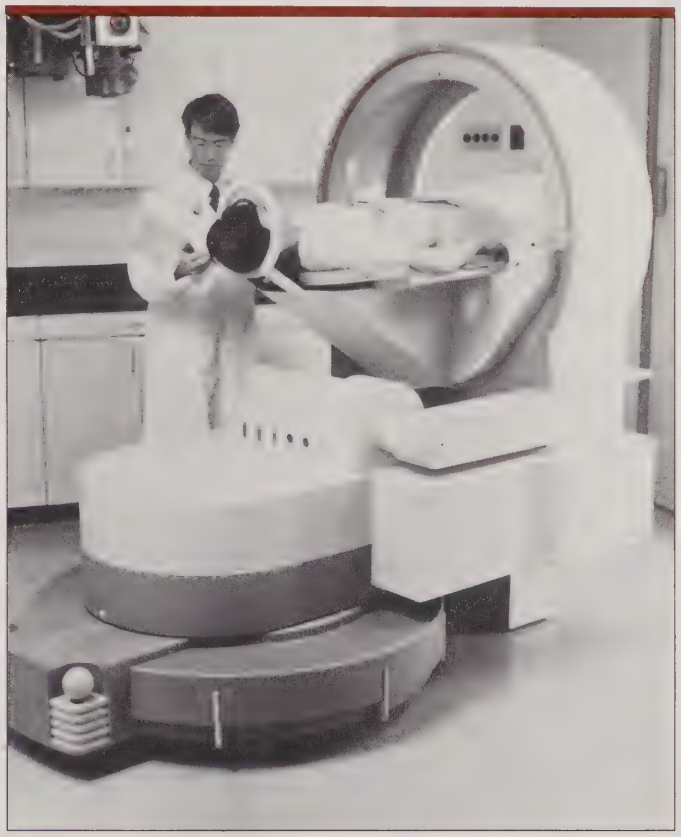
"What we set out to do was to take advantage of the qualities of the proton beam, which are really favorable to treatment compared to these other types of radiation, by using modern imaging," Dr. Chapman said.

"In theory that sounds easy to do. But in practice it was a big deal and involved a lot of engineering tricks that had never been tried before."

The STAR unit is essentially a space-age mobile bed. A patient lies on the bed where his head is fixed in a halo-like ring rigidly attached to the positioner.

The bed can be moved along five different axes so that the target is aligned with the isocenter of the beam (the point where the beam has its highest energy). A patient restraint system holds the patient comfortably in the bed during the procedure.

"Once the target and isocenter are aligned, the axes of rotation pass through the target very precisely so that no matter how we move the patient, the target stays right on the proton beam," Dr. Chapman said. "It is extraordinarily precise. We can move a patient to a position in space that is accurate to microns. Dr. William Butler, a neurosurgical resident working on the project, jokingly said it was accurate enough to be able to kill a single bacteria."



*A "patient" is shown installed in the STAR unit Patient Positioning System.*

The joke is telling.

"Right now the only limitation on the accuracy of the unit is the imaging," Dr. Chapman said. "At the present time the imaging is nowhere near that accurate. But I expect that will improve as well.

"That's what I think is so important about this machine. It's really been designed for the future rather than the present. It will still be up-to-date 10 years from now."

Design engineers think so too. The unit has already won awards for design excellence in both national and international competitions. In 1990 the Industrial Designers Society of America awarded PGI and the machine a bronze medal. In its annual 1991 awards issue, *International Design Magazine* awarded PGI an International Design Selection Award for the unit.

Neurosurgeons began using the unit to treat patients earlier this year. So far its use has been limited to patients with metastasized brain tumors (cancers that have spread).

"We started out treating those patients first because there are so many of them and such a need to do something for them immediately," Dr. Chapman said. "And the chances of success in controlling their tumors locally with the proton beam are very high."

Other treatment applications will include arteriovenous malformations (a mass of abnormal blood vessels in the brain), pituitary tumors and other benign tumors of various types that either cannot be treated surgically or have failed surgical treatment.

"It is also possible to perform so-called 'functional treatments' where you make a lesion in some part of the brain in order to improve a condition," Dr. Chapman said.

Tic douloureux, for example, is a condition characterized by pain in the face. It is often treated by making radiofrequency lesions with a needle in a nerve at the base of the skull. Neurosurgeons are now discussing the possibility of delivering high doses of proton beam radiation to the nerve to relieve the pain.

"Some of these treatments aren't on the table yet, but they are all things we are thinking about," Dr. Chapman said. "There are a tremendous number of applications for the machine. I believe this is the design of the future for sophisticated radiosurgery facilities."

Currently there are only two other proton beam cyclotrons in the U.S. being used for medical treatments. Both are in California. One is at Berkeley, which three years ago, shut down the world's first proton beam cyclotron and shifted its medical operation to another accelerator at the same institution. The other is a brand new unit at Loma Linda University. Worldwide there are 16 medical proton beam cyclotrons. Another 16 are on the drawing boards. ■

## — 'Sick Building Syndrome' a Growing Problem

*(Continued from Page 1)*

Health Associates — will be on education and the prevention of occupational disease. As part of this emphasis, group practitioners will be making house calls on sick buildings and other workplaces with known or potentially hazardous exposures.

"We're not a group practice in the sense that we exist primarily to see patients," said L. Christine Oliver, MD, Director of Occupational Health Associates. "We exist primarily to prevent work-related illnesses and diseases by focusing on workplaces in distress — workplaces where there are identified or suspected illnesses or diseases that are thought to be related to the workplace itself."

The emphasis on prevention is a natural for the new group practice. Ernesto Gonzalez, MD, an MGH dermatologist, said work-related skin diseases alone cost American businesses more than $1 billion in claims each year.

"Most of these diseases are not life-threatening so we don't hear too much about them," Dr. Gonzalez said. "But in terms of their cost to the economy, it's very high."

Treatment of work-related skin diseases usually involves drugs to alleviate the symptoms and separating the worker from the irritating substance — or if possible, removing the substance from the environment altogether.

"But even when employees are removed from that work environment, studies show that up to 60 percent of them will continue to have that specific problem," Dr. Gonzalez said. "In other words some chemical reaction is occurring in the body so that once the process starts it self-perpetuates even when the incriminated substance is removed.

"That's why prevention is so important. If we could go out to the worksite and identify the problems or the potential problems before they happen, it will obviously save the workers a lot of grief and the industry a lot of money."

Roughly one fourth of all reported occupational illnesses and injuries are skin related, according to 1989 figures compiled by the U.S. Department of Labor. Another large category of complaints is associated with musculoskeletal problems — back pain, neck or shoulder strain, knee injuries, fractures, etc.

"One third of all workers' compensation claims are musculoskeletal related," said Edwin T. Wyman, MD, an MGH orthopedic surgeon and member of Occupational Health Associates. "The best way to treat these injuries is to prevent them by evaluating the workplace for situations that are likely to cause a certain musculoskeletal complaint and then fixing them."

These kinds of workplace adaptations are called "ergonomics" — making the physical plant better fit the human body. Often, Dr. Wyman said, ergonomic solutions are simple: adjustable work stations, conveyer belts that eliminate lifting, forklifts to move materials, education courses on proper lifting techniques, or even physical fitness classes to strengthen muscles used in lifting. "By spending a couple of thousand dollars, a company can potentially save hundreds of thousands of dollars in workers' compensation claims," Dr. Wyman said.

While a back injury, a skin rash, or a lung disease such as asbestosis can be traced fairly easily back to the worksite, other occupational diseases such as those caused by inadequately ventilated buildings are more subtle and harder to diagnose.

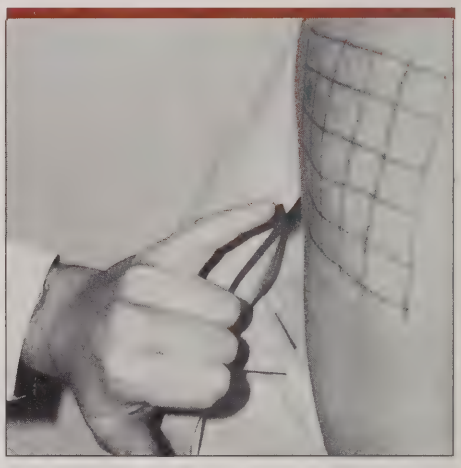
Symptoms can often be vague — fatigue, nose and eye irritations, headaches, dry throat, dry skin, etc. Occupational asthma is another example of a common disease with often unsuspected occupational or environmental causes.

In order to trace the problems back to the worksite, doctors must first take a good workplace history and then rule out other causes of observed symptoms.

"What's required for the workplace is the same type of evaluation that's required for an individual patient," Dr. Oliver said. "The difference is that the history-taking involves the history of a whole group of workers as well as some history of the workplace itself."

The diagnosis also involves a physical examination of workers and worksite, as well as laboratory tests of both workers and worksite. (The latter is usually done in conjunction with engineers or certified industrial hygienists who will test the adequacy of the ventilation and other building systems and measure airborne levels of toxic substances.) When all the history-taking and tests are complete, recommendations for treatment are made. Sometimes the solution is as simple as eliminating smoking from the workplace; other times, the solution is more complex — a new ventilation system, eliminating or substituting chemicals used at the plant, modifying equipment or work practices to reduce musculoskeletal stress, etc.

One of the largest projects Occupational Health Associates is undertaking involves the development and implementation of a health examination and occupational disease surveillance program as part of a pilot project to provide comprehensive primary health care to the New England members of the Laborers International



*Joanne Fennell, LPN, (not shown) removes a contact dermatitis test patch from the back of a patient. Each patch contains a different chemical. In the photo at right, Ms. Fennell points to a positive reaction to one of the chemicals.*

## A Rash Solution

OCCUPATIONAL diseases can happen anywhere, anytime to almost anyone. Consider the Boston Bruins.

"About 10 years ago, several National Hockey League players, including some of the Bruins, started developing rashes all over their bodies," said Ernesto Gonzalez, MD, an MGH dermatologist called in by the Bruins to investigate the problem for the Boston team. "They were so incapacitated by the skin rashes, many could not function as players. The team was very concerned."

After several tests and evaluations, Dr. Gonzalez finally isolated the irritating substance — fiberglass in the hockey sticks used by the players.

"Before every game I noticed the players would hit the ice with their sticks," Dr. Gonzalez said. "This caused little fiberglass needles on the sticks to come loose and spray into the air. They'd get stuck onto the players' uniforms, giving some of them a rash."

The solution? New sticks and no more banging the ice before games. ■

Union of North America.

The three-part program includes individual occupational disease surveillance for asbestos, lead, and hazardous waste workers, primary health care, and health education. The 550,000 member Laborers union — one of the largest in the building trades — is made up of a wide variety of construction workers involved in everything from asbestos abatement to bridge building.

"This is a group of workers whose health care needs have historically been underserved," Dr. Oliver said. "They've had a myriad of exposures, yet they haven't really been carefully examined with regard to occupational illness and disease or for risk factors associated with other types of medical problems.

"It's also a group of workers in whom stress-related issues haven't been looked at very carefully."

Treating work-related stress is now a recognized component of occupational medicine practice. Of all occupational hazards, stress is the most pervasive, causing medical illness directly and indirectly by promoting unhealthy lifestyles, as well as affecting organizations' productivity.

"The classic description of the individual susceptible to stress is the Wall St. executive-type," said Andrew Littman, MD, Director of the Behavioral Medicine Clinic at the MGH Cardiovascular Health Center and a member of Occupational Health Associates. "But that's a myth. Stress can affect people in all job descriptions."

Symptoms include a feeling of impatience, frustration, anger, and anxiety. Stress can also manifest itself in physical ailments. "A person's stress level is not necessarily proportionate to the stressful event, especially when it comes to work-related stress," Dr. Littman said. "People value their work environments and are invested in them. Subtle shifts in terms of autonomy, responsibility, control over one's environment, the manner and style of management, can all have profound effects on individuals."

Although psychiatrists may offer ways of treating stress, prevention remains the treatment of choice among most occupational health experts.

One of the most effective of these approaches is called "cognitive behavioral psychotherapy." This method involves learning how to identify stressful situations and individual signs of stress and then learning tools to adequately deal with those situations and feelings. .

Another remedy involves organizational changes brought about through consultations with internal management.

"These are very effective interventions for reducing symptoms of stress," Dr. Littman said.

Occupational medicine is also rapidly expanding into the area of environmental medicine.

"More and more we're seeing in our practice patients who are concerned about environmental disease," Dr. Oliver said. "Either disease emanating from chemicals in the environment — a hazardous waste dump, a factory, a sewage plant — or diseases resulting from low level exposures to chemicals and pollutants inside a building.

"So environmental medicine and occupational medicine really are merging and becoming one field."

And like occupational medicine, prevention is a key component in battling environmental disease.

"More and more, industry recognizes that preventing these problems — whether it's lung disease, low back pain, stress, a skin disease, or some other problem — from occurring in the first place is better than after-the-fact treatment," Dr. Gonzalez said. "That is the message we want to get out to industry. It's better to prevent these problems than to treat them after they happen." ■

*Kristine Nelson Tesar, RN, (left) and Christie Kuo, RN, lead a stress reduction class at the MGH Cardiovascular Health Center.*

# Expansion, Change Marked McCluskey Years

OUTGOING MGH Pathology Chief Robert T. McCluskey, MD, presided over a period of great change and expansion during his 17 years at the helm of the department.

A mild-mannered man with a reputation for fairness, Dr. McCluskey was a firm administrator, admired by his staff and colleagues.

During his tenure, he expanded the entire Pathology Department, particularly updating technology and strengthening research. He also increased the number of staff pathologists and residents, encouraged subspecialization, and undertook several new initiatives, including the consolidation of all the hospital's clinical laboratories to make patient care even better.

"He is a superb administrator," said Eveline E. Schneeberger, MD, recruited by Dr. McCluskey in the mid-70s to direct the Electron Microscopy Research Unit.

"He is a very fair, courteous man," added Atul Kumar Bhan, MD, newly named Director of the Immunopathology Unit which Dr. McCluskey greatly expanded. "I have seldom seen him lose his temper. He is always a gentleman, always has a sense of humor."

Like Dr. Schneeberger, Dr. Bhan was recruited by Dr. McCluskey from Children's Hospital in Boston.

Dr. McCluskey served as Chief of Pathology at Children's from 1971 until coming to the MGH in1974.

"He's the reason I came here," Dr. Bhan said. "I wouldn't have come if he hadn't been here. I think that's true of others in the department as well."

Although Dr. McCluskey did recruit several pathologists, including Michael Laposata, MD, PhD, from the University of Pennsylvania to head the hospital's clinical laboratories, he also reached from within to build the department.

"My goal in building the staff was to strike a balance between outside and inside talent, and I hope a balance between people whose primary skill is diagnostic work and people whose primary interest is research," Dr. McCluskey said.

The balance between "inside" and "outside" talent and diagnosis and research was perhaps most strikingly achieved in the Immunopathology Unit, which expanded from a small space on Warren 2 onto the fifth floor of the Cox Building.

From 1980 until this year, the unit was headed by Robert B. Colvin, MD, a career-long MGH pathologist. It was following Dr. Colvin's appointment as **Chief of the Department** *(see Page 1 story),* that Dr. Bhan was named Director of Immunopathology.

Under Dr. McCluskey's direction Immunopathology at the MGH also expanded as a diagnostic discipline.

"One of the first areas in which immunologic techniques were used diagnostically was in kidney diseases," Dr. McCluskey said. "During the 1960s we learned that the diagnosis and classification of kidney diseases was improved through the detection of immunoglobulins [immune-system defenders called antibodies] which accumulate in particular patterns within the kidneys in several diseases."

The emphasis on immunopathology during Dr. McCluskey's tenure mirrored his own research interests.

An internationally known renal pathologist, Dr. McCluskey was particularly interested in immunologically mediated kidney diseases. These are conditions in which the patient's immune system plays a role in the disease process.

"The immune system is designed to protect the host," Dr. McCluskey explained. "But sometimes — using the same mediators that can eliminate invading bacteria or viruses — the immune response can actually produce disease, as has been convincingly shown to occur in several forms of renal disease."

Because of Dr. McCluskey's pioneering work in this area, the scientific and medical community has a better understanding of the complex mechanisms involved in the development of these conditions.

Much of his research has been performed in collaboration with members of the Renal Unit of the MGH Department of Medicine. Recently he and John Niles, MD, a member of that unit as well as of the Department of Pathology, have developed tests for circulating autoantibodies against neutrophils (these are antibodies directed against a person's own white blood cells), which are virtually diagnostic of certain serious but treatable forms of glomerulonephritis — diseases affecting the kidney's filtering structures necessary for the formation of urine and the preserva-

*Dr. Robert T. McCluskey*

tion of renal function.

A major expansion of research in the Department of Pathology occurred in 1988 when James T. Kurnick, MD, and others established a research unit in the Lawrence E. Martin Laboratories at Charlestown, the MGH's off-campus research center.

Another hallmark of the McCluskey years was the increasing subspecialization of the department. Although he did not start the trend, he certainly encouraged it. Today, the MGH has some of the most highly regarded pathology experts in the country. "All of the staff have some area of expertise," Dr. McCluskey said. "I encouraged this even though there was some opposition to it when I came to the MGH.

"Some people felt it was important to maintain the skills of general surgical pathology. I agree with that. But at the same time, in order to provide the kind of diagnostic information and the kind of care our patients expect, I felt it was necessary to increase the move toward subspecialization."

Dr. McCluskey was born in New Haven, Conn. in 1923. He graduated from Yale University and received his medical degree from New York University School of Medicine. For many years he was on the faculty of that medical school.

Before coming to Boston, he was Chairman from 1968 to 1971 of the Department of Pathology at the State University of New York in Buffalo.

During his long tenure at the MGH, he held several academic appointments at Harvard Medical School, most recently as the Benjamin Castleman Professor of Pathology, a chair named in honor of his predecessor as MGH Pathology Chief.

Dr. McCluskey will retain that chair at Harvard and continue his research in the MGH pathology laboratories in Charlestown. ■

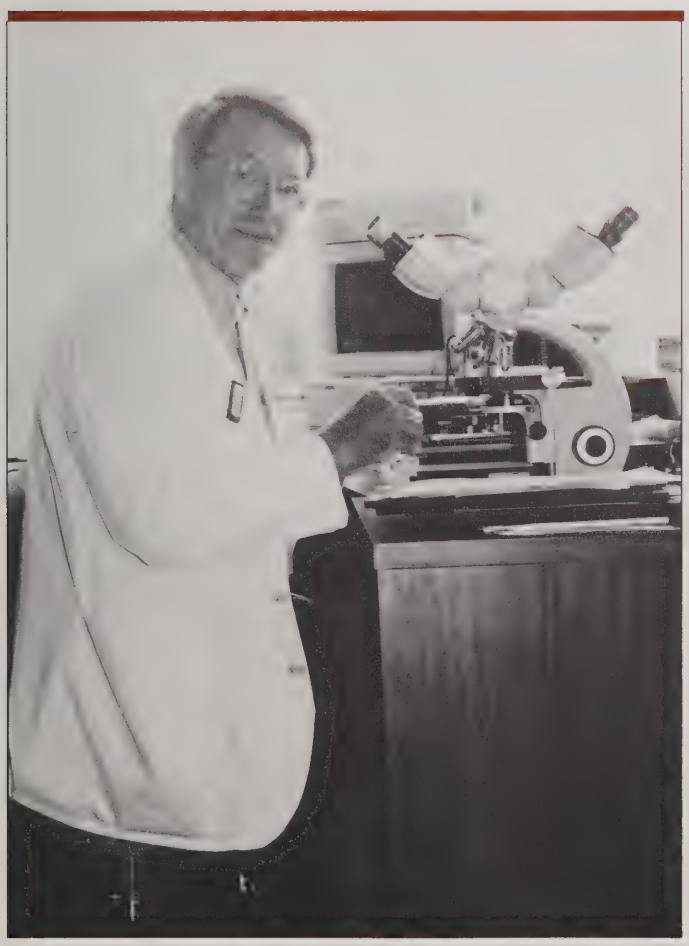
## — New Pathology Chief

*(Continued from Page 1)*

"From this one small piece of material we are able to do all sorts of studies. We can look at the cells; we can study them with antibodies [defenders against foreign cells] to determine the type of molecules that are present. There is just a remarkable number of things that we can measure now that we couldn't measure 10 or 20 years ago," said Robert B. Colvin, MD, newly named Chief of the MGH Department of Pathology.

"Molecules are being discovered left and right and many of them are being linked to disease processes. Our techniques are also becoming much more sophisticated. We are moving beyond simply using the light microscope to techniques that allow us to take more of a molecular diagnostic approach in order to get at the bottom of what is happening in the tissues.

"And that's the challenge that lies ahead for pathologists — to evaluate and integrate all of this new knowledge and these new technologies in a way that will be useful and beneficial to the patient."



*New MGH Pathology Chief Dr. Robert B. Colvin*

In the case of the kidney transplant patient, the pathologists discovered that the young man was having a reaction to cyclosporine, a drug used to suppress a transplant recipient's immune system in order to prevent rejection of the donor organ.With this information his doctors were able to adjust the patient's medication. Within hours he began to improve.

Most patients will probably never see or meet a pathologist. Pathology is the study of disease processes either after death through autopsies or in living patients through biopsies. A pathologist is more likely to carry a microscope than a stethoscope; to be found in a laboratory than an examining room. Yet his findings and opinions are critical to accurate diagnosis — and very often to treatment decisions. When it comes to diagnosis, the pathologist more often than not has the definitive word.

"We're not just laboratory workers," Dr. Colvin said. "We are doing something that contributes in a very substantial way to diagnosis. We have to be accurate. We have to get the information out as quickly as possible. And we have to be able to communicate our understanding of the patient's problem to the clinicians."

Dr. Colvin's own career is a testament to the power a pathologist can have on patient care.

A "homegrown boy," Dr. Colvin began his tenure at the MGH as a surgical resident in 1968 following his graduation from Harvard Medical School. As a young resident he was inspired by Paul S. Russell, MD, founder and recently retired Chief of the MGH Transplantation Unit *(MGH News, March 1991)*, to apply his interest in immunology and kidney disease to the then new field of transplantation.

"I've always been interested in kidney disease," Dr. Colvin said. "When I was a resident, kidney disease was being studied by the most sophisticated techniques we had then in pathology, and I was attracted by that. The kidney is also often the target of the immune system whenever that system gets out of line. At that time the kidney was also the only organ being transplanted.

"So it was natural that as I got more and more interested in immunology and kidney disease, I would also get involved in transplantation."

Over the years — first as a resident, then as a staff pathologist, and for the last 11 years as Director of the MGH Immunopathology Unit, Dr. Colvin has enjoyed a long and fruitful collaboration with the MGH Transplant Unit.

*(Concluded on Page 8)*

## — Pathology Chief

*(Concluded from Page 7)*

He was a key member of the team headed by current Transplantation Chief A. Benedict Cosimi, MD, in the development of OKT-3, a monoclonal (single cell) antibody used to treat graft rejection. The MGH was the first institution in the world to use monoclonal antibodies to treat patients. OKT-3 is now widely used around the world to treat graft rejection in transplant patients.

Currently Dr. Colvin, again in collaboration with Dr. Cosimi and the MGH Transplant Unit, is investigating ways to block the adhesion (stickiness) of cells to one another following transplant surgery.

"One event that's very fundamental to the way cells recognize tissue as foreign is the way they bind to each other," Dr. Colvin said. "So we think if we can interfere with that stickiness of cells in a very selective way by blocking just the right adhesion molecules, we can affect the rejection process in a very profound way."

The blocking agent the investigators are using is an antibody to ICAM-1 (Intercellular Adhesion Molecule Number 1).

"ICAM-1 is a molecule on blood vessel cells which is the target of the graft rejection process," Dr. Colvin said. "They're also on certain other cells. We found that if we give this ICAM-1 antibody to monkeys who had kidney grafts, we could block these cells from binding to each other and greatly prolong the survival of the kidney graft."

So far preliminary patient trials with the new blocking agent have also looked very promising. "There's a lot of work still to be done," Dr. Colvin cautioned. "But at this point it looks like it's one of the important molecules in preventing graft rejection."

The new blocking agent also has important implications for patients suffering heart attacks or other kinds of heart damage caused by myocardial ischemia (decreased blood flow to the heart due to narrowing of the coronary arteries). Part of the damage in these conditions occurs when blood reenters the heart, inflaming and injuring the blood vessels.

"It turns out that some of the same adhesion molecules involved in graft rejection are also involved in this process," Dr. Colvin said.

The ICAM-1 molecules on the damaged blood vessels bind with receptors on inflammatory cells circulating in the blood. "So when the returning blood brings these inflammatory cells into the heart, they bind with the damaged blood vessels, enhancing the damage. If we can block that adhesion, we might be able to prevent that further damage from occurring," Dr. Colvin said.

Research in this area is still preliminary, Dr. Colvin said. But experimental studies appear promising.

"Ultimately our goal as pathologists is to improve therapy and diagnosis," Dr. Colvin said. "That is our primary goal in everything we do — to improve patient care."

To accomplish this mission Dr. Colvin has set forth a number of goals for the MGH Department of Pathology.

Over the last 10 or 15 years the department's biopsy and surgical load has about doubled. As the department has grown in size, it has also specialized.

"We're fortunate in our institution that we're big enough to have an expert in virtually every area of pathology," Dr. Colvin said. "I want to encourage the development of that expertise. At the same time I'm very interested in bringing people together and giving them a sense of teamwork even when they have many different interests."

Dr. Colvin also wants to further strengthen and expand the department's residency program which recently added new positions to bring the number of pathology residents to 27.

"We have wonderful residents; outstanding morale," said Dr. Colvin, who is also Professor of Pathology at Harvard Medical School. "With the richness of our environment, I believe we have the potential to train even more people here."

Building the hospital's molecular pathology unit is also a goal.

"The most important and significant change that is occurring in pathology is that we are becoming more molecular in our diagnostic techniques. Because of this I think the field is attracting a group of people who are very scientifically oriented; who like using the modern techniques. And it's an area I want to strengthen and build because it's where the future lies."

Dr. Colvin inherits a department that is no stranger to breakthroughs and innovation.

From the discovery of appendicitis to the discovery of the origin of blood platelets, the MGH Department of Pathology has a long and distinguished record.

As a "homegrown boy" who has spent his entire career here, the new chief brings a deep appreciation of these traditions and achievements to his new position. "It's very easy to take over this department from such outstanding pathologists who I've known since the very start of my medical career, who trained me and have influenced me so much over the years," Dr. Colvin said. "It's incredibly exciting and a very great honor." ■

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# Cultured Skin Cells: Band-Aids of the Future?

BAND-AIDS in the future may no longer be kept in the medicine cabinet in the bathroom. They will more likely be found in the freezer next to the frozen peas.

"When somebody has a wound, we'll just open up the freezer, pull out a package of skin, and warm it up in a little room temperature water," said Jessica Fewkes, MD, Co-director of the MGH Dermatologic Surgery Unit. "It'll be the ultimate bandage — a kind of bioactive Band-Aid to make wounds heal up faster and better."

Since 1982 when G. Gregory Gallico, MD, an MGH plastic surgeon, and Nicholas E. O'Connor, MD, of Brigham and Women's Hospital, first used cultured skin cells to treat a massively burned patient at the Shriners Burn Institute, the use of cultured epithelial cells as a wound dressing has continued to expand.

Doctors now use large pieces of living skin cultivated from less than a square inch of tissue that has been frozen and then thawed to treat burn victims, skin cancer patients, and a growing array of dermatology patients.

Epithelium is the covering of all internal and external surfaces of the body. When doctors refer to cultured epithelial cells, however, they are really referring to one type of cell — the human keratinocyte — which is the primary cell type of the epidermis, the outermost layer of skin.

From a handful of these human keratinocytes taken from a skin donor site about the size of a postage stamp, scientists can grow enough epidermis —

*(Continued on Page 4)*

# *Epilepsy Center Getting Off the Ground*

WHEN EPILEPSY specialist Daniel Hoch, MD, PhD, set up his MGH office hours, he figured he would be able to see most of his epilepsy patients on one day.

"Originally I thought I would have an epilepsy clinic on Wednesdays, and then on Fridays I would see patients with more generalized neurological problems," he said.

"But within several days of giving the secretary my clinic spots, both days were filled with epilepsy patients. It's obvious that two days is not going to be enough, but it's a start."

According to the journal *Epilepsia,* 6 people out of every 1,000 suffer from some kind of epileptic seizure, a temporary disturbance of brain function. In two of these six people, the seizures are poorly controlled.

Recognizing the need for specialized epilepsy care at the MGH, newly appointed Neurology Chief Anne B. Young, MD, PhD, *(MGH News, June 1991)* has established as one of her first goals here

*(Continued on Page 2)*

INSIDE

***Sitting on Top of the World***

*Eleven years ago Catherine Krumme of Winchester, Mass. was diagnosed as having acute lymphocytic leukemia. Since then doctors have made dramatic strides in curing this common childhood cancer. Above, Catherine, now 15 and off chemotherapy for more than 4 years, is shown on top of 14,255-foot Long's Peak in Colorado. "ALL has become a disease we expect to win," say Catherine's MGH doctors. Story, Page 7.*

EDITORIAL

# New Frontiers for Viewing the Brain

THE COVER OF THE NOVEMBER 1 *Science* magazine shows a remarkable color image of a person's brain while it was processing information. That is the first time scientists have been able to demonstrate in one session with clarity (high resolution) what parts of the brain come into play during mental activity. The information being processed was from watching a flashing light, and red and yellow demonstrate the portions of the visual cortex involved.

Scientists from the MGH-NMR Center (Department of Radiology) in Charlestown, led by John W. Belliveau, PhD, and Bruce Rosen, MD, PhD, conducted the trail-blazing study. To make such images the group used a special MRI (also called NMR) device that works much faster than traditional MRI. They made their image possible by experimentally combining the device with use of a harmless agent that causes the parts of the brain involved with seeing the flashing light to be contrasted in a unique way with brain areas not involved. Unlike other imaging techniques MRI employs no radiation.

The speed of the MRI made on a General Electric device with a special fast accessory from Advanced NMR Systems, Inc., of Wilmington, Mass., offers many new possibilities. In addition to showing blood flow, blood volume, and use of oxygen in the brain, the new device can produce clear images of other parts of the body. Now, for example, physicians can produce good images of the beating heart without resorting to difficult or radioactive techniques. Children are unable to undergo ordinary MRI because of the length of time — up to 45 minutes or more — they have to remain still while in the slow device. The short scan time of seconds should open the new device to children. And the same short scan time promises to reduce the cost of an MRI examination. The MGH has been the only institution experimenting with the new device since a crude form of the scanner became a research tool.

As often happens in research, 11 days after the *Science* article another group of scientists reported their own unique images of the brain, this time taken when a person was remembering a word. The team at Washington University in St. Louis used a different device called PET (positron emission tomography) for its images. (Washington University and the MGH were the first institutions to experiment with an earlier form of positron emission in the 1950s.) PET employs radiation to produce its images while MRI uses a powerful magnet. PET has had a longer history of experimentation with brain images, so that the results with MRI are more unexpected.

Both MRI and, to a lesser degree, PET, have been available for years to diagnose illnesses. The MGH-NMR group, under Thomas J. Brady, MD, is already employing its newly innovated technique with fast NMR to carry out improved means of diagnosis. Now the studies reported last month in Boston and St. Louis are creating excitement in the scientific world. Scientists appear to be on the threshold of unlocking secrets of how the brain works. That alone will likely make relevant academic textbooks outdated in a few years. Ultimately those findings should further revolutionize the practice of neurology, neurosurgery, and psychiatry to the benefit of patients everywhere. ■

## — Epilepsy Center

*(Continued from Page 1)*

the creation of an Epilepsy Center.

Dr. Hoch spent the last four years as a fellow and resident in clinical neurophysiology at the University of California at Los Angeles which has one of the country's leading epilepsy centers. He has been recruited by Dr. Young to help develop the MGH center.

Along with John W. Stakes, MD, Director of the MGH All Night Sleep Laboratory, and Clinical Neurophysiology Fellow Frank G. Gilliam, MD, Dr. Hoch is already seeing patients in the newly formed MGH epilepsy outpatient clinic.

In addition Dr. Hoch is assisting in the care of inpatients who have been admitted to the hospital for other reasons — stroke, diabetes, a heart condition, etc. — but who also have seizures or experience seizures while in the hospital.

"The first thing I want to do is find out more about the patients that the hospital already has who have epilepsy," Dr. Hoch said. "The people in the neurology department have been treating patients with epilepsy for years, and my job is to find out where those patients are, who they are, and how refractory [uncontrollable] their seizures have been."

As part of this learning process and as a way of improving patient diagnosis and care, Dr. Hoch intends to purchase new epilepsy monitoring equipment for the

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hospital.

"We have new methods for looking at seizures and detecting seizures," Dr. Hoch said.

These new machines and monitoring equipment are sophisticated and sensitive enough, for example, to differentiate between real epileptic seizures and so-called psychogenic seizures, which are distinguished by their lack of electrographic activity (i.e. they are psychic in origin rather than organic).

"Psychogenic seizures don't respond to antiepileptic medications for obvious reasons — they're very, very different from epileptic seizures," Dr. Hoch said. "But they do tend to respond very well to psychosocial measures: cognitive therapy, psychotherapy, antidepressants, and so forth.

"So for patients with these types of seizures, and more importantly for patients who have both types of seizures, which is the most common scenario, diagnosis is crucial."

Accurate diagnosis is also crucial in determining what type of epileptic seizure a patient is having — where in the brain the electrical activity is emanating. "Seizures that start focally in one part of the brain and spread around the brain may respond very differently to medications than seizures that start all over the brain at once," Dr. Hoch said.

Recent advancements in the treatment of epilepsy underscore the importance of accurate diagnosis.

Surgical treatment of epilepsy continues to advance and become more routine. Medical treatment of epilepsy has also greatly improved. Fast disappearing are the days of random drug treatment of epilepsy. Now a systematic approach to treatment based on accurate diagnosis and knowledge of drug mechanisms of action is used.

"Pharmacologically we're starting to see some of the basic science research having to do with the mechanisms of epilepsy come to fruition," Dr. Hoch said. "There is a whole batch of new, exciting compounds waiting in the wings, probably more than we've ever had before, poised and ready to come onto the market."

Getting the MGH involved in some of these upcoming patient trials that will be testing the effectiveness of these new compounds is one of Dr. Hoch's goals for the new Epilepsy Center. "There is a small percentage of people who don't respond to any treatments that we have now. Getting these patients involved in some medication trials is very exciting, and I think will help a lot of people."

An epileptic seizure occurs because of defects in neurotransmitter activity in the brain. Neurotransmitters are chemical messengers that, when released, either excite or inhibit the target cell.

An example of how an epileptic seizure might occur would be an inhibitory neurotransmitter that because of a defect fails to stop a cell in the brain from "firing."

"That cell may just fire again and again, and then it recruits other cells and you've got a seizure," Dr. Hoch said. "The other side of that story would be what happens if there's a problem with the excitation? There's too much excitation rather than too little inhibition.

"The truth is certainly a combination of both of those. There are excitatory and inhibitory amino acids {building blocks of proteins} that probably play a role in the generation of a seizure and probably also in the cell damage that occurs during seizures and also during strokes."

After spending several years in the laboratory investigating some of these basic mechanisms involved in seizures, Dr. Hoch is anxious to apply what he has learned to help patients.

"The kind of areas that I'm hoping to do clinical research in are very much related to what I did in the lab," he said.

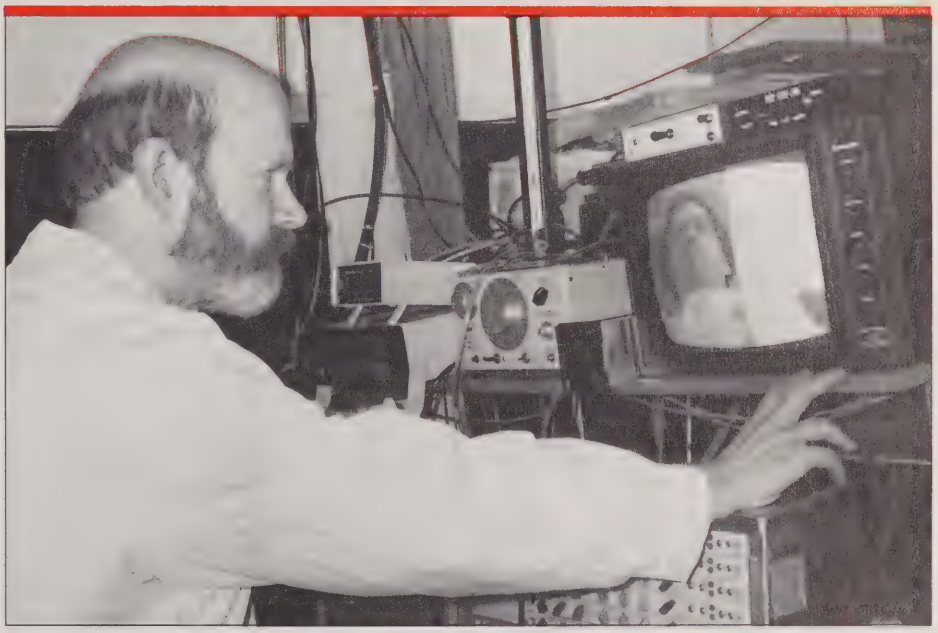
Designing effective patient trials of new drugs is one area where Dr. Hoch hopes to merge his laboratory experience with patient research.

"Having an idea of what's going on biochemically can help guide a well-designed clinical trial and a well-designed application in the Intensive Care Unit," he said. "For instance, status epilepticus [continuous seizing without regaining consciousness between seizures] after cardiac arrest — which is not an uncommon event — can be very difficult to treat and adds to the damage that's already been done by the cardiac arrest.

"Having some knowledge of how these compounds have been generated in the basic science laboratory can certainly help and guide decisions about what's a reasonable clinical trial to get involved in."

In addition to drug trials, Dr. Hoch also wants to do clinical research in epilepsy at the MGH in collaboration with other investigators and physicians already here.

He pointed to work being done in laboratories at the MGH on animal models of epilepsy and cell damage. Other MGH investigators, for instance, are studying the cerebral spinal fluid in conjunction with research on diseases such as Huntington's and Alzheimer's. "In humans cerebral spinal fluid can be used for similar biochemical studies of epilepsy," Dr. Hoch said. "The connecting interest we all share is excitatory amino acids. I think there are some basic science activities and collaborations here that are certainly common and possible."



*Epilepsy specialist Dr. Daniel Hoch adjusts a polygraph machine in the MGH All Night Sleep Laboratory. The polygraph measures a patient's brain wave activity, eye movement, respiration, muscle movement, heart rate, and oxygen saturation. Doctors use this machine to study sleep and seizure activity during sleep.*

Other possible areas of collaboration are stroke and PET (positron emission tomography).

"MGH has many of the components of an outstanding epilepsy center already here," Dr. Hoch said. "It has an excellent neurosurgical department, an excellent neurophysiology department. My goal is to help bring all these components together." ■

## — Cultured Skin Cells: Band-Aids of the Future?

*(Continued from Page 1)*

enough outer layer of skin — to cover an entire human body. Howard Green, MD, now of Harvard Medical School, and his graduate student James G. Rheinwald, PhD, developed the technique for cultivating the cells in the laboratory. They reported the advance in November 1975.

"These cells are generated from the patient's own skin so there's no problem with transmission of disease from one patient to another or of immunologic rejection," Dr. Gallico said.

The year after Drs. Gallico and O'Connor applied cultured epithelial cells on a child at Shriners, across the street from the MGH campus, they grafted five more patients using the Rheinwald-Green cultivation technique.

Despite their benefits, however, cultured epithelial cells have only recently gained wider use in burn care. Split thickness skin grafting (replanting both the epidermal and underlying dermal layers of skin) remains the treatment of choice for all but the most massively burned victims who do not have enough donor sites for split thickness grafting.

The labor intensiveness involved in cultivating the cells at first hindered wider use and acceptance of the cultured skin technique.

"The problem in the beginning was that you needed a lab dedicated to doing nothing else but producing these cells because the cultivation process has to be balanced with the patient-care demands," Dr. Gallico said. "You had to immediately move into graft production as soon as a patient presented himself; then you had to be able to balance the maturity of the grafts as they were growing in culture with the readiness of the patient to go to the operating room to receive them. It was quite a feat to juggle all these variables and to meet clinical demands."

In 1986, Dr. Green and his colleagues and others founded BioSurface Technology, Inc., in Cambridge, Mass. The private company produces cultured epithelial cells commercially and has helped overcome some of the early problems of supply and demand.

Instead of needing to have a highly specialized laboratory on site to culture cells sporadically, burn surgeons and others using the technique, could now send epidermal cells from a patient to BioSurface, where the cells are cultivated and the grafts returned to the surgeon.

BioSurface now ships grafts to most major burn centers in the U.S., France, and Germany.

But widespread availability was only one factor holding back greater acceptance and application of cultured skin during its early history. Another was its "take" or success rate.

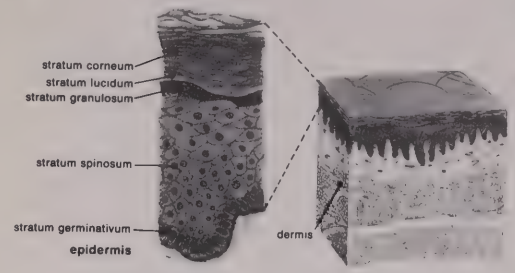
In a comprehensive study published in 1990 comparing patients with giant congenital nevi (birth marks) treated with split thickness skin grafts and those treated with cultured skin grafts, Drs. Gallico, O'Connor, and John P. Remensnyder, former Chief-of-Staff at the Shriners Burn Institute and now Director of the MGH Operating Rooms, were able to document the exact take rate for the two procedures. They found that split thickness skin grafts had an 84 percent success rate, compared to 68 percent for cultured skin grafts. "We felt those results compared pretty favorably to the standard method of treatment," Dr. Gallico said.

In another study, published in 1989, on the long-term effects of cultured skin, Carolyn C. Compton, MD, PhD, an Associate Pathologist at the MGH who has a joint appointment at Shriners, examined biopsies of 21 burn and congenital nevi patients treated with cultured skin grafts. In long-term patients (those with cultured skin grafts up to five years after surgery), Dr. Compton found indications of the development of lower-layer skin (dermis) from what otherwise would be scar tissue.

"The keratinocytes themselves are very biologically active cells, and it seems that when you transplant them back to the wound bed they are able to modulate wound healing of the connective tissue beneath them to the point of inducing the regeneration of dermal tissue," Dr. Compton said. "Eventually on long-term followup, that's what we see. We don't see tissue that looks like scar tissue, which is what you would expect to see in a big cutaneous wound. We see connective tissue that looks like dermis beneath these cultured epithelial cells."

That observation contradicts conventional belief that dermal cells cannot regenerate.

*In reality many scientists now agree that burn care will likely be only a small part of the future of cultured epithelial cells. Their broadest application may be as a biological dressing — either temporary or permanent — for more chronic, stubborn wounds rather than acute, life-threatening wounds.*




At the MGH, for instance, Dr. Gallico has pioneered the use of cultured skin autografts (tissue cultured from the patient's own cells) to treat giant congenital nevi. These large birth marks can cover 50 percent or more of a patient's body.

Dr. Fewkes has been using cultured autografts to treat a wide variety of skin cancer patients, as well as nonhealing wounds such as venous stasis ulcers (lower leg ulcers).

"It's a very exciting advance for people with a large loss of skin for whatever reason," Dr. Fewkes said. "It's very easy to apply, relatively easy to take care of, and gives you a source of skin that won't go away because you can freeze these cells and take them out and culture them when you need them."

Far down the road, scientists are also studying the possible use of cultured epithelial allografts (skin grown from the epidermal cells of another person rather than the patient). This technique has particularly exciting implications — despite the problems of rejection associated with transplanting foreign tissue — because scientists have discovered that the cultured skin graft does not need to take permanently to have an effect on healing.

"Cultured keratinocytes are so biologically active that even if they are rejected, the few days in which the graft sits on top of the wound is enough to stimulate the wound to heal from epithelial cells at its periphery and in the wound bed, despite the fact that these cells have never been stimulated by conventional therapies to close that wound," Dr. Compton said.

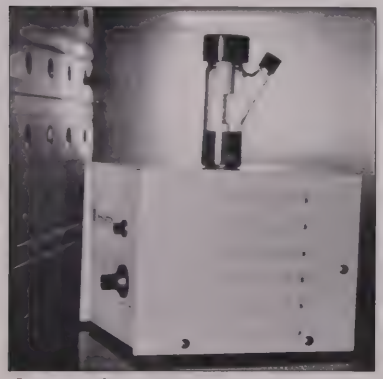
Investigators at the MGH and elsewhere are already studying the use of epithelial cells cultivated from the foreskins of circumcised infants as a dressing for chronic wounds.

"BioSurface Technology, Inc., has developed the method to freeze grafts, keep them frozen, and then thaw them out and use them whenever they are needed," noted Dr. Gallico, who is also a Consultant in Surgery at Shriners. "Allografts give you the possibility of having a frozen wound dressing ready as a skin graft substitute at all times."

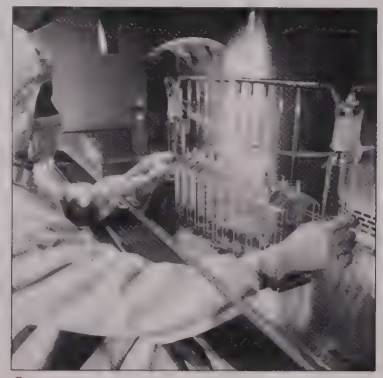
At Boston University School of Medicine, Tania J. Phillips, MD, Assistant Professor of Dermatology, is using epithelial cells cultivated from neonatal foreskins as an experimental dressing for venous stasis ulcers.

Two possible approaches to the problem of rejection of allografts include: 1) preventing the cultured skin graft from being rejected until after biological factors in the graft have stimulated neighboring epidermal cells to close the wound spontaneously; and 2) using the allografts in conjunction with mild immunosuppression drugs. The drugs would suppress the patient's immune system enough to allow the grafts to take permanently over the wound.

"As we continue to improve the technology and the take rate of the grafts, it opens up a lot of possibilities down the road for all kinds of wound dressings," Dr. Gallico said. "It's gone way beyond what we originally envisioned in 1982." ■



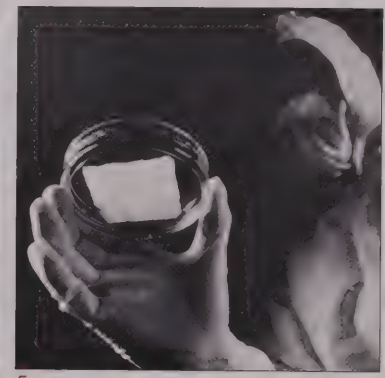
*1 A patient biopsy (tissue) is trimmed and reduced to single cells.*



*2 Each cell culture flask is "gassed" to maintain the proper balance of acid-alkalinity (pH) for optimum cell culture.*

*3 The cultured epithelial autograft is gently teased away from the bottom of the flask.*

*4 The graft is attached to a petrolatum (a petroleum jelly-like substance) impregnated gauze carrier and prepared for transportation to the patient.*



*5 A cultured epithelial autograft ready to go onto a patient.*

# Simple Tool Helps Identify At Risk Children

A 1989 survey by the Institute of Medicine, part of the National Academy of Sciences, found that about 12 percent of all school-age children may go on to develop a behavioral or emotional disorder.

This risk substantially increases among children of psychiatric patients. Although exact figures are not available, research indicates that nationally the children of adult psychiatric patients are at two, three, or even four times the risk of suffering an emotional disorder as the children of nonpsychiatric patients.

There are many reasons for this increased risk. Genetic factors, the impact of being raised by an emotionally disordered parent, and secondary stressors, such as poverty, divorce, or a parent's hospitalization for mental illness, can all play a role in creating a dysfunctional child.

Despite their increased risk, however, these children often do not receive the psychiatric attention and care that they need.

"Adult psychiatrists receive some training in child psychiatry, and certainly they're interested in the ability of their patients to function socially and as parents. But how well the children are functioning is often not a central focus of the adult patient's visit to a general psychiatric clinic," said Michael S. Jellinek, MD, Chief of the MGH Child Psychiatry Service. "Adult psychiatrists don't have the time, the focus in some cases, or the necessary training."

A simple, five-minute screening tool developed by Dr. Jellinek may help in the recognition of these children's problems. The 35-question checklist, administered to parents in the waiting room of an adult psychiatry clinic, is designed to help the adult psychiatrist identify patients with at risk children. The adult psychiatrist can then, if needed, refer those children to a child psychiatrist for further evaluation.

The questionnaire, known as the Pediatric Symptom Checklist, was developed more than 10 years ago by Dr. Jellinek and J. Michael Murphy, PhD, a staff psychologist in the MGH Department of Child Psychiatry.

Initially the researchers conceived the PSC as a tool to help pediatricians identify at risk children in their practices. Over the years, Dr. Jellinek and Dr. Murphy have expanded the use of the PSC to other patient populations. The most recent study was designed to test the questionnaire's effectiveness in screening at risk children in an adult-oriented psychiatric practice.

"We knew we couldn't expect all psychiatrists caring for adults to take thorough histories in terms of child psychiatric functioning," Dr. Jellinek said. "But what we were hoping was to be able to give them a screening tool that would help these psychiatrists know which kids may need further attention."

To conduct the study, researchers handed out the checklist to 100 parents in the waiting room of the MGH Adult Psychopharmacology Outpatient Clinic. They found that the rate of positive scores (indicating an at risk child) to be twice that of a pediatric office practice.

The PSC is a "gentle" 35 questions that parents answer either "sometimes," "often," or "never."

Questions are also simple: "Does your child daydream too much?" "Act as if driven by a motor?" "Have difficulty with teachers?" "Have aches and pains?"

Answers are scored zero points for "never," one point for "sometimes," and two points for "often."

"If the score is 28 or above, that school-age child has a high likelihood of having some kind of psychosocial dysfunction," Dr. Jellinek said.

Extensive research, including a number of interviews with family members of dysfunctional children and comparisons to other screening instruments, helped researchers arrive at the 28-point cutoff.

Although other instruments and questionnaires are available to identify at risk children, Dr. Jellinek said none are as short and easy to answer and score as the PSC. He estimated it takes about three to four minutes for a parent to take the test, and about one minute to score it.

"Other questionnaires will give you more information but take at least 20 minutes to administer and may involve some computer scoring," Dr. Jellinek said. "Ours won't give you as much information, but the real use of the PSC in a psychiatric practice is routine screening. It is not meant to give you a diagnosis. We think that depends on a clinical evaluation, not on a paper and pencil test. What the PSC is meant to do is to highlight the fact that somebody should spend some time thinking about how this child is functioning." ■

## Pediatric Symptom Checklist

**Please mark under the heading that best fits your child. (Ages 5 to 13)**

| | | Never | Sometimes | Often |
|---|---|---|---|---|
| 1 | Complains of aches or pains | | | |
| 2 | Spends more time alone | | | |
| 3 | Tires easily, little energy | | | |
| 4 | Fidgety, unable to sit still | | | |
| 5 | Has trouble with a teacher | | | |
| 6 | Less interested in school | | | |
| 7 | Acts as if driven by a motor | | | |
| 8 | Daydreams too much | | | |
| 9 | Distracted easily | | | |
| 10 | Is afraid of new situations | | | |
| 11 | Feels sad, unhappy | | | |
| 12 | Is irritable, angry | | | |
| 13 | Feels hopeless | | | |
| 14 | Has trouble concentrating | | | |
| 15 | Less interest in friends | | | |
| 16 | Fights with other children | | | |
| 17 | Absent from school | | | |
| 18 | School grades dropping | | | |
| 19 | Is down on him or herself | | | |
| 20 | Visits doctor with doctor finding nothing wrong | | | |
| 21 | Has trouble with sleeping | | | |
| 22 | Worries a lot | | | |
| 23 | Wants to be with you more than before | | | |
| 24 | Feels he or she is bad | | | |
| 25 | Takes unnecessary risks | | | |
| 26 | Gets hurt frequently | | | |
| 27 | Seems to be having less fun | | | |
| 28 | Acts younger than children his or her age | | | |
| 29 | Does not listen to rules | | | |
| 30 | Does not show feelings | | | |
| 31 | Does not understand other people's feelings | | | |
| 32 | Teases others | | | |
| 33 | Blames others for his or her troubles | | | |
| 34 | Takes things that do not belong to him or her | | | |
| 35 | Refuses to share | | | |

**Score: 0 Never; 1 Sometimes; 2 Often**
**A score of 28 or above, consult your pediatrician.**

# *Childhood Leukemia: 'We Expect to Win'*

As the crow flies it is a mere 10 miles from the MGH Pediatric Oncology Clinic to Winchester, a suburb northwest of Boston.

But when you travel that route every week and sometimes every weekday for three years, 10 miles can seem a lifetime. Especially if you are seven years old.

"We used to devise all sorts of games in the car because we spent so much time there," Cynthia Krumme said.

On this particular trip in 1984, however, Cynthia's seven-year-old daughter, Catherine, had put the games away. It was Catherine's first trip back to the MGH since the Krummes had received the news that Catherine's leukemia had returned. She had suffered a relapse. Another three years of stepped-up, intensified treatment faced her.

On the ride back to the clinic for her first treatment since suffering the relapse, Catherine wrote down some "rules" for the next three years.

The "Clinic Rules" Catherine Krumme presented her MGH doctors and nurses in 1984 still hang on the wall of the clinic. And while the "rules" of the clinic have not changed in the nearly eight years since Catherine wrote them down, the chances of surviving leukemia — even after a relapse — have improved significantly.

"We've made dramatic strides over the last few years," said William S. Ferguson, MD, Chief of the MGH Pediatric Hematology-Oncology Unit. "For many of us childhood leukemia has shifted from a disease in which we expected to lose and were pleasantly surprised when we won, to one in which we expect to win and usually do."

Catherine Krumme was on the leading edge of those changing expectations. As a four year old in 1980 with acute lymphocytic leukemia, she had a 50-50 chance of survival. A four year old with ALL today would have about an 80 percent chance of being cured. Even more significantly, the rate of recovery from a relapse has greatly improved. Ten years ago, a relapse was a very pessimistic diagnosis. Doctors pegged Catherine's chances of recovery after a relapse at about 15 to 20 percent. Today, she would have a better than even chance of a cure.

Acute lymphocytic leukemia accounts for more than 90 percent of all childhood leukemias. An uncontrolled growth of an immature white blood cell, ALL strikes 1 in 20,000 children between the ages of 2 and 5. Early warning signs include bruising easily, fatigue, and paleness. Sometimes a child may complain of bone or joint pain as well. Cause of the disease is unknown.

Although ALL is now the most successfully treated leukemia, that was not always the case.

"The designation 'acute' reflected the fact that in prechemotherapy days the time from diagnosis until death was relatively short, and the only question was how long we could sustain a child before death," Dr. Ferguson said. "It was a very rapidly progressing disease."

Chemotherapy has greatly changed the lives of children with ALL. Over the last 10 years, doctors have altered their treatment of ALL very little. For most children treatment consists of a three-year regimen of chemotherapy administered orally, intravenously, and intramuscularly. The drugs are given in three phases, beginning with a one-month "induction" phase, followed by an "intensification" phase, and rounded out by a "maintenance" phase.

If the overall treatment regimen has not changed, the intensity has.

"Once children have gotten into remission — and almost every child gets into remission after about a month — the trend has been to treat them with a period of very intense chemotherapy for about two to six months," Dr. Ferguson said. "With

*(Concluded on Page 8)*

***From left:*** *Catherine Krumme, 4, at the beginning of her leukemia treatment in 1980.*

*Catherine with Monica Corrigan, RN, one of the nurses in the MGH Pediatric Oncology Clinic. The photo was taken in 1981.*

*Catherine and her older brother, Matt, this summer on a hiking trip in Colorado.*

*(Concluded from Page 7)*

this regimen we've gotten to the point where the low risk, or standard risk, child has a chance of cure that's close to 80 percent."

One of the most striking aspects of leukemia treatment — at least to an outsider — is the normalcy with which children can carry on their lives.

"Catherine's doctors called it the MGH theory of getting well," Mrs. Krumme said. "Do everything as normally as possible."

"It doesn't do much good to cure patients of leukemia only to have them scarred in other ways," Dr. Ferguson added. "By and large the children are able to carry on normal lives, and we encourage them to do so."

Although Catherine missed most of nursery school because of a threat of contracting chicken pox, which is particularly dangerous to children with leukemia, she started kindergarten with her peers and has remained in step with them.

"A week before she started kindergarten, she lost her hair because of the chemotherapy," Mrs. Krumme said. "Some children don't lose their hair, and Catherine didn't lose hers for the first year, so we thought we were going to avoid that. But then a week before school began, her hair began falling out. So in addition to the trauma of starting school, she also had the trauma of losing her hair."

In the second grade, after her relapse necessitated an intensified round of chemotherapy combined with radiation, Catherine lost every hair on her head and had to wear a wig.

"Losing my hair didn't seem to bother me that much," Catherine said. "I remember going over to a friend's house and popping off my wig whenever it got too hot. I never did that in school, but my friends didn't seem to mind."

If losing her hair did not bother her, coping with the fatigue — another side effect of chemotherapy — was more difficult. But Catherine would put her head down on her desk and after a few minutes would be fine. Throughout her treatment she played soccer, basketball, sang in the chorus, and made the honor roll.

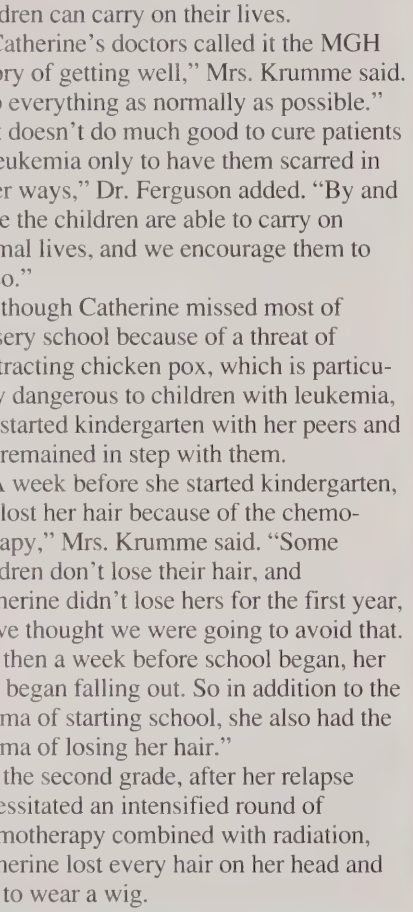
Catherine has been off treatment now for four years and four months. With every passing month the chances of her leukemia remaining in remission improve.

"The general feeling now is that if a child's leukemia remains in remission seven years, the chances of the leukemia coming back are extremely small — not zero — but extremely small," Dr. Ferguson said.

The long-term effects of chemotherapy also appear small. The walls of the MGH Pediatric Oncology Unit attest to just how small. Pictures of the hundreds of children who have passed through the clinic's doors adorn the walls.

In many ways the walls resemble a family album. And with each passing year and improvement in outlook, the album gets bigger and bigger. There are photos of birthdays, graduations, proms, weddings, births, each accompanied by a hand-scrawled note.

"It's always nice to see kids years off treatment coming back to visit with their own kids in tow," Dr. Ferguson said. "It's something that 20 years ago, no one would have dared hope or think. Now we see it all the time." ■



Clinic Rules

1. Must have a good sense of humor.
2. Must always go a good L.P. B.M.
3. Must always remember the chickenpox.
4. Must tell the truth to anyone who wants it.
5. Must like people
6. Must like junk food
7. Must know a lot about chemotherapy
8. Must not mind the sight of blood
9. Must like bald heads
10. Must never be grumpy.

*The "Clinic Rules" seven-year-old Catherine Krumme presented her doctors in 1984 still hang in the MGH Pediatric Oncology Clinic.*

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# MGH to Offer Obstetrics Through Vincent Memorial

OBSTETRICS, long the missing service at the MGH, will soon be missing no longer.

Beginning in October 1994, obstetrical care will be offered at the MGH through the Vincent Memorial Obstetrics and Gynecology Service, the women's care division of the general hospital.

The delay in starting the service results from the hospital's space crunch. With no room on the current campus, the new service must await the completion of the second phase of the hospital's 10-year inpatient bed replacement program. Workers broke ground on that second building last fall. It is slated for completion October 1, 1994.

"A lot of members of our community would like the obstetrical unit to open immediately, but there's simply no space right now," said Isaac Schiff, MD, Chief of what until 1994 remains the MGH-Vincent Memorial Gynecology Service.

The new unit will have 21 inpatient beds, several labor and delivery rooms, a room for caesarian sections, and several sleep rooms for the doctors on call. The unit is being built to handle about 2,000 deliveries a year.

Although the Vincent Memorial has been a gynecological hospital since its founding more than

*(Continued on Page 4)*

*Dr. Veronica Ravnikar, Director of the Vincent Infertility and Menopause Unit, is shown with Claudia E. Simon and her two children, Emma (left) and Ian. Mrs. Simon became a patient of Dr. Ravnikar after difficulty having a second child.*

*Lights, Camera, Action*

## *Patient Trial Tests New Light-Activated Cancer Drug*

A PROMISING new cancer fighting drug that can be turned on and off with the flick of a light switch is the subject of a first-in-the-nation patient trial at the MGH.

BPD-MA, a "second generation" light-activated drug, has shown promise in treating tumors in animals. The U.S. Food and Drug Administration (FDA) recently approved the drug for use in humans with skin cancer as part of a clinical study to be conducted initially at the MGH. The first patients in that study were admitted to the MGH in November.

***Doctors involved in the trial stressed that it is far too early to know whether the experimental treatment will work in humans.***

BPD-MA (benzoporphyrin derivative-monoacid ring A) is a light-sensitive drug whose cancer fighting properties are released only when light is shined on the drug. The combination of light (lasers) and drugs is known as photodynamic therapy (PDT).

"The basic concept of photodynamic therapy [also known as photochemo-therapy] is that you give a patient a drug that is completely innocuous without the light," said R. Rox Anderson, MD, an MGH dermatologist who is heading the current trial.

Although there is considerable research currently under way at the MGH and other major laser centers around the world on different types of photodynamic

*(Continued on Page 2)*

INSIDE

*Mistake Leads to Important Study*
*See Page 7*

EDITORIAL

# The Joy of Obstetrics

NEWBORN BABIES bring with them a special joy that transcends their effect on parents and relatives. Push a baby carriage down the street, and the carriage's occupant attracts the eager stares of passersby. Whether it's in a store or restaurant, or any public place, a mother carrying an infant fascinates onlookers. Smiles and even baby talk are directed at the newborn by elderly strangers who for a moment become young again.

There is no place where a newborn baby attracts more happiness than a general hospital. In an atmosphere where illness predominates, the arrival of a healthy newborn commands the greatest cheer. (Especially so in a teaching hospital where the other patients tend to be so sick.) The contrast of a little, warm, pink somebody reminds us of the (outside) world where a relatively small percentage of people are seriously ill. For others the newborn is a reminder of how important it is to take care of one's health. Visitors unhappy to see a friend who is quite sick can also be moved by seeing the newborn. Perhaps those who are the most gratified by the sight are health workers themselves. Caring for a healthy newborn is a particular treat.

It is with this special quality in mind that the just-announced news of the planned return to the MGH of obstetrics has caused such positive reaction at the hospital. Nearly 40 years has been too long for the MGH to be without obstetrics. Not only will obstetrics prove a mood elevator but the MGH also has a lot to offer expectant mothers and their newborns. A page 1 article describes many of these advantages: a highly regarded Newborn Intensive Care Unit for those new arrivals who enter life with a major health problem; an excellent infertility unit that until now has had to send its successful patients elsewhere to deliver; a major infertility research center, one of two in the country that the government has just funded; strong pediatric and pediatric surgery services, and a variety of research into obstetrics-related fields, to name some. For those expectant mothers who are already under the care of MGH specialists, it is comforting to know they can have their babies where their doctor is close at hand. Finally, for the communities near the MGH, the closeness of an obstetrical service will be a convenience. No community is closer than the more than 200 MGH employees or spouses now forced to deliver each year in other hospitals.

This news comes at a time when the Vincent Club, a critical supporter of the Vincent Memorial Hospital for women's care, which will carry out obstetrics, enters its 100th year. The Club has raised millions of dollars for the Vincent in the century of its existence and had fun with its labor-intensive annual fund-raising play. And the Vincent Memorial has just completed its first century. The renaissance of obstetrics could not have come at a better time. ■

## New Light-Activated Drug

*(Continued from Page 1)*

cancer therapies, no new compounds have yet come on the market. The closest to winning government approval is Photofrin II — the predecessor to BPD-MA. This "first generation" drug has been used experimentally in humans for several years at a few hospitals including the MGH.

In a study published November 12, 1987, in the *New England Journal of Medicine*, George R. Prout, Jr., MD, now retired Chief of the MGH Urology Service, reported the results of a patient trial he conducted in the People's Republic of China using Photofrin II to treat bladder cancer. Although the results of that trial were promising, Dr. Prout concluded that more patient trials were needed.

Photofrin II and its more promising successor, BPD-MA, are derived from a class of compounds called "porphyrins." Porphyrins are light-sensitive molecules found naturally in all humans. The porphyrins used in photodynamic therapy are found in the bloodstream. "They're the part of the hemoglobin molecule that makes our blood red," said Harvey Lui,

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MD, a Research Fellow in dermatology. "It has been found that if you take blood and extract the porphyrin, the porphyrin can be used as a drug."

But as a drug, porphyrin becomes active only when light is shined on it. "If the light doesn't hit it, nothing happens," Dr. Anderson said.

In the case of Photofrin II, however, the tissues surrounding the tumor remained photosensitive for up to six weeks after the initial exposure to the drug-activating laser light. Patients suffered first and second degree burns after simply a few minutes exposure to natural light. This persistent photosensitivity has been a major limiting side effect of Photofrin II.

Unlike Photofrin II, which is basically a derivative of bovine hematoporphyrin (cow's blood porphyrin), BPD-MA is a semi-synthetic compound.

"The drug company looked at the porphyrin molecule and tried to figure out where you needed to put certain chemical groups in order to give the molecule certain properties," Dr. Lui said.

And one of the most important properties researchers wanted to give the new drug was the ability to bind to the tumor cells while "clearing" the normal cells as quickly as possible.

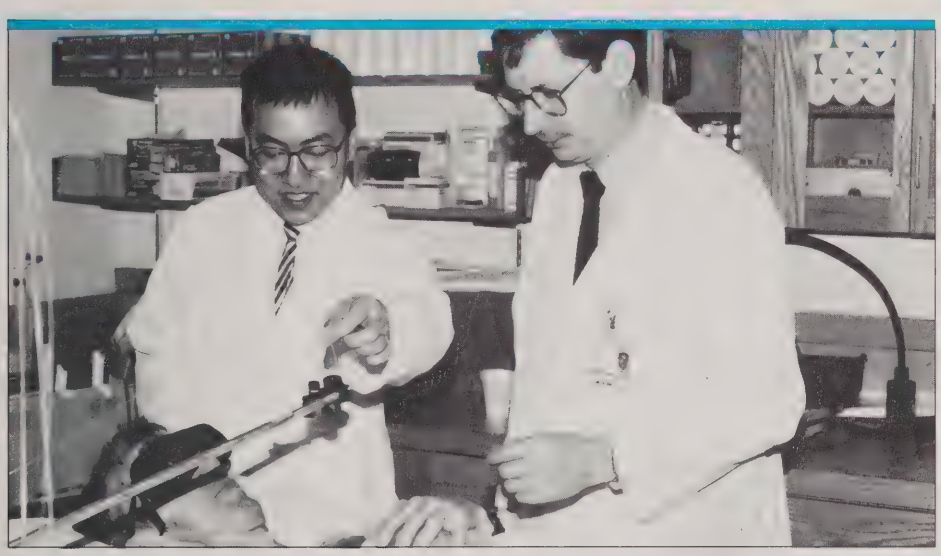
"It was the Photofrin's persistence in the normal skin that made people photosensitive from four to six weeks after treatment," Dr. Lui explained.

In animal studies BPD-MA causes significantly less photosensitivity than Photofrin II with no loss of effectiveness.

Theoretically scientists can activate the drug with any light. "The fact that a patient who's given Photofrin II goes out in the light and comes back with first and second degree burns means that ordinary visible light is sufficient to activate the drug," Dr. Lui said. "The problem with ordinary light is that the treatment is limited to the organs you can access using light."

Instead doctors activate the drug with lasers. By coupling the laser light to a fiber optic tube (delivery system), they can get the light from the source outside the body to the site of the treatment area. Because lasers are high-intensity light sources, exposure times for patients are greatly reduced. And finally lasers provide doctors a choice of light colors for maximum effectiveness.

"Porphyrins have specific properties that react differently to different colors of light," Dr. Lui said. "By using laser light, we can pinpoint where the natural absorption of the porphyrin is and then tailor our light to that point."



*Drs. Harvey Lui (left) and R. Rox Anderson explain the laser procedure to Travis L. Brown. Mr. Brown, of Winslow, Me., was the first patient admitted into an MGH trial that is studying the effectiveness of a new light-activated cancer drug.*

Researchers have found that BPD-MA is most effectively activated with red light, which is also the most effective light for penetrating tissue. "If we were treating psoriasis or something fairly superficial, we might not necessarily use red light because you don't need to get deep penetration," said Dr. Anderson, who is also Research Director of the MGH Dermatology Laser Center. "But we're not treating psoriasis, we're treating tumors, so we need deeper tissue penetration, which is why we use the red light."

The timing of the light exposure will be one of the major questions researchers will be studying in the MGH trial. "You want to give the light exposure at the time when the drug is most concentrated in the tumor tissue and least concentrated in normal tissue," Dr. Anderson said.

Determining the proper drug dosages is another goal of the trial. The MGH group, which also includes hematologists-oncologists David C. Harmon, MD, and Irene Kuter, MD, PhD, of the MGH Cancer Center, has been approved to test the drug in up to 40 patients.

Three categories of patients will be considered for inclusion in the study. They include patients with an internal cancer such as breast or lung cancer that has spread to the skin (cutaneous metastases). Other patients will have primary skin tumors, either basal cell or squamous cell carcinomas. Those with basal cell carcinomas must undergo surgical removal of the treatment site, as well as receiving the drug. No surgery will be required for the other cancers. Up to three skin tumors per patient will be treated. Patients will be admitted to the hospital for four days for treatment, and then followed regularly for three months. There is no control group. All participating patients will receive the drug and will be treated free of charge.

Currently the MGH is the only institution in the country approved to study BPD-MA in humans. The hospital was selected to carry out the studies because of its pioneering work in photodynamic therapy and also because of its location which should guarantee a wide patient population for the study. Dr. Anderson estimated this Phase I clinical trial will last about a year. If successful, experimental use of the drug will likely expand to other organs and centers.

BPD-MA was developed by QLT Phototherapeutics, Inc., a Canadian pharmaceutical company. QLT is underwriting the costs of the MGH trial.

Although the immediate goal of the current study is to compare BPD-MA to Photofrin II — the only other light-activated cancer drug currently being tested in humans — the long-term implications of the trial are potentially more far-reaching.

"In the big picture we're interested in this drug because we want a way to treat cancer locally without having a limit on the number of doses that you can give," said Dr. Anderson, who is also Associate Professor of Dermatology at Harvard Medical School. "In chemotherapy and radiation therapy you have a limiting dose that the tissue can stand. And if you reach that limit and you still haven't gotten rid of the tumor, then that's it.

"The porphyrins, on the other hand, do not have any harmful genetic [mutagenic] effect on cells. In theory we should be able to go back and use this drug over and over and over again. So that's another very exciting aspect to this study. But only time will tell whether theory proves to be reality." ■

# MGH to Offer Obstetrics Through Vincent Memorial

*(Continued from Page 1)*

a century ago *(see accompanying story)*, that hospital, and before that, the MGH, did offer obstetrical care for several years.

The service was actually an extension of the Boston Lying-In Hospital, the obstetrical hospital which later came together with the Free Hospital for Women in Brookline to form the "women's" portion of the Brigham and Women's Hospital. Obstetricians from the Boston Lying-In Hospital staffed the MGH unit, traveling across town to deliver their patients. Sometimes the baby arrived before the obstetrician.

"It was not unusual in a rapid delivery for the patient to be delivered by the house staff here," said George S. Richardson, MD, Associate Chief of Service at the Vincent. "At that time the house staff was not obstetrically trained. They were all in the process of training for general surgery. So for them it was somewhat out of their realm to be suddenly confronted with the delivery of a baby since they did not normally assist the obstetrician in the OR. The visiting obstetrician was assisted by the nursing staff."

Ultimately, the lack of specialized obstetrical care and the small number of patients, combined with an increasing demand for surgical beds, led the MGH to abandon obstetrical care in the early 1950s.

Nevertheless, over the years some pregnant women, particularly newcomers to Boston, no doubt taking note of the name Massachusetts *General* Hospital, have arrived here on the verge of giving birth.

"It is not unusual for a woman who has had no prenatal care to take a taxi to the MGH when she goes into labor as she looks to us to deliver her," Dr. Schiff said. "We do an average of one delivery a year in the Emergency Department because a patient will be so close to delivery that we cannot transfer her fast enough to an obstetrical unit in another hospital.

"People go to a general hospital expecting all aspects of their health care to be provided. At the MGH obstetrics is an exception. Clearly, it has been a missing service."

In addition to fulfilling the promise of its name, the MGH is reinstituting obstetrical care for several other reasons. Chief among them, said J. Robert Buchanan, MD, General Director, is the desire to provide the full spectrum of care to all of the hospital's patients.

"Many women receive their care at the MGH from experts in diabetes or hypertension or some other condition," Dr. Schiff said. "When these women conceive, they wish to be followed by their own doctors and not be referred elsewhere for their obstetrical care."

The Vincent is also a major center for the study and treatment of infertility. The new obstetrical unit will be a natural extension of that function.

***Left:*** *Dr. Schiff in the operating room.* ***Right:*** *The Vincent-Burnham Building is located in the shadow of the hospital's new Ellison Building.*

"If we took only the obstetrical patients who have achieved their pregnancy as a result of our infertility service, we'd have quite a fair number of deliveries," Dr. Richardson said.

In April the infertility unit of the Vincent Gynecology Service will expand even further with the addition of in vitro (test tube) fertilization techniques.

"The decision to begin offering IVF was made separately from and before the obstetrics decision," Dr. Schiff said. "But obviously as one unit grows, it helps the other.

"When our patients achieve pregnancy through our infertility unit or through the outstanding care given by other services at the MGH, they become frustrated when they cannot deliver here. Now they will have the opportunity and satisfaction of remaining at the MGH."

The new obstetrical service will also have important teaching and research components. The MGH is the original and largest teaching hospital of Harvard Medical School. "Many of the physicians who come through the MGH for their training go on to become professors of medicine and surgery throughout the country," said Dr. Schiff, who is the Joe Vincent Meigs Professor of Gynecology at Harvard Medical School. "Yet they may depart without ever having seen a pregnant woman during their training. We know that there are some conditions that are different in pregnant women than in nonpregnant women. For example appendicitis."

In a pregnant woman, the pain from appendicitis is felt in the right upper quadrant of the abdomen. Normally appendicitis pain is in the right lower quadrant of the abdomen.

"Obstetrics will thus be a major addition to our teaching program," Dr. Schiff said.

Dr. Schiff believes research at the MGH will also be greatly expanded with the addition of the new obstetrical service.

"Genetics and prenatal diagnosis are important new avenues of research that will hopefully allow us to determine methods of avoiding congenital or family inherited disorders," Dr. Schiff said.

*Isaac Schiff, MD, Chief of the MGH-Vincent Memorial Gynecology Service*

*In utero* surgery — operating on the fetus while it is still inside the mother's womb — is one example of the possibility of combining prenatal diagnosis with pediatric surgical skills to solve a problem before a child is born.

"We plan to collaborate very closely with Dr. Patricia K. Donahoe, Chief of Pediatric Surgery, and her team as well as with all of the experts we have here at the MGH," Dr. Schiff said.

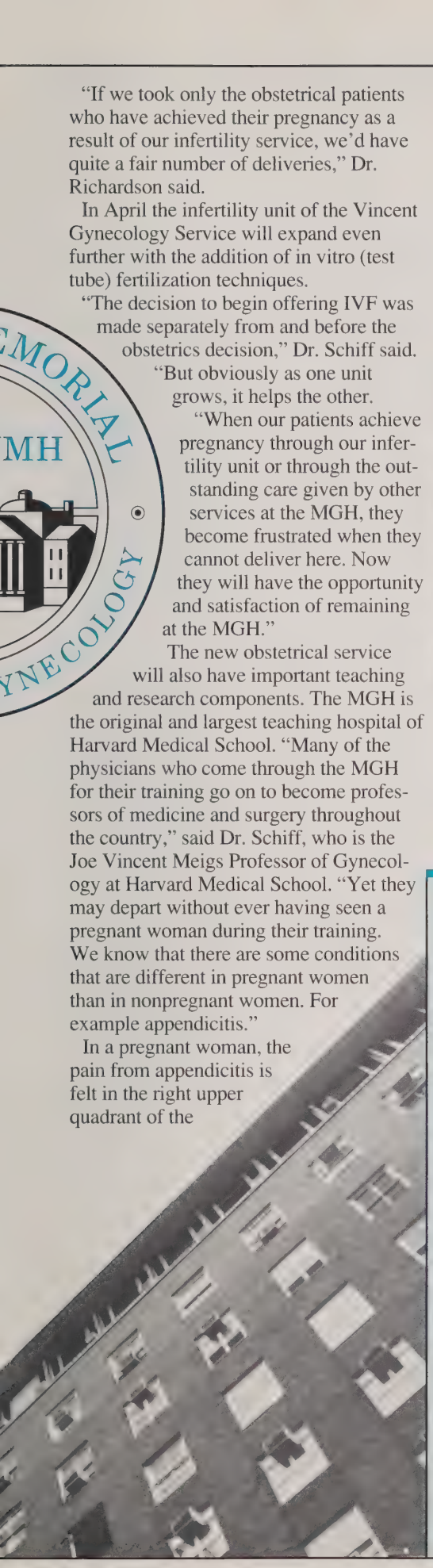
"We're all very, very thrilled and pleased that the Mass. General has decided to get back into obstetrics through the Vincent," said Lewis H. Clark, Chairman of the Vincent Board of Trustees. "The Vincent certainly is looking forward to sponsoring the service. With the great staff that we have here, it's very appropriate that an obstetrical unit be added to the outstanding gynecological service that is already here."

"I'm very enthusiastic about the new service," said W. Nicholas Thorndike, Chairman of the MGH Board of Trustees. "It puts the MGH back in the arena of being a general hospital providing all services. I think it will invigorate the staff."

Dr. Schiff believes the addition of obstetrics will change the whole mood and character of the hospital.

"A patient coming into the hospital for any kind of service who sees a mother leaving the hospital with a newborn child could not help but experience joy.

"We will all feel younger and more upbeat." ■



# Vincent Memorial Service Unique in Women's Care

FROM a women's hospital staffed entirely by women, to a women's hospital staffed mostly by men general surgeons, to a women's hospital staffed by specialists of both sexes, the Vincent Memorial Service, the gynecological (and soon to be obstetrical) unit of the MGH, has come a long way.

Internationally known for its research and treatment of women's diseases, particularly cancer in women, and for its pioneering work in treating infertility in both sexes, the Vincent continues to move aggressively into its second century of operation.

In April the hospital will expand its already extensive infertility services by adding in vitro (test tube) fertilization techniques to be directed by Veronica Ravnikar, MD.

In addition Isaac Schiff, MD, Chief of the Vincent Memorial Gynecology Service, has announced that the hospital will begin offering obstetrical care in 1994, following the construction of an expanded facility in the second phase of the hospital's 10-year inpatient bed replacement program. *(See Page 1 story.)*

The announcement of the new services coincides with the 100th anniversary celebrations of the Vincent Club, the major private fund-raising organization of the hospital. Founded two years after the hospital itself, the Vincent Club has a membership of 1,300 women from around the country. Over the years the club has raised more than $6.5 million to support the hospital's research and training programs.

"We are certainly very excited with the changes," said Mrs. William S. Friend, President of the Vincent Club. "As a private women's organization that has *(Concluded on Page 6)*

# — Vincent Memorial Service Unique in Women's Care

*(Concluded from Page 5)*

spent the last 100 years supporting women's health care and services, we think it is especially appropriate that the gynecology service is now going to be a complete service for women. It makes our cause all the more worthwhile and gives us an incentive to work harder in the future."

The Vincent Hospital was founded on Dec. 12, 1890, by friends of Mrs. James R. Vincent as a memorial to the well-known Boston actress. Dedicated to the treatment of "the diseases of women," the hospital was originally located at 44 Chambers St. in Boston's West End, not far from its present location on the MGH campus.

For much of its early history the staff of the Vincent was composed solely of women. In 1919 Daniel Fiske Jones, MD, became the first man to join the regular staff.

By 1940 the hospital had outgrown its facilities. Recognizing the need for modern surgical and laboratory techniques and equipment, the Trustees of the Vincent accepted the invitation of the MGH to become its gynecological unit while retaining its own corporate identity. In 1947 the Vincent moved into its present location on the first three floors of the Vincent-Burnham Building.

Although it has always been dedicated to gynecology, the Vincent actually evolved out of the MGH Departments of Surgery and Medicine.

"Until the arrival of Dr. James H. Nelson [the first board-certified Ob-Gyn specialist to head the Vincent] the department trained general surgeons in the area of gynecology," said George S. Richardson, MD, Associate Chief of Service at the Vincent, who himself trained at the Vincent as a general surgeon during the 1940s.

Nevertheless, the Vincent made many important advances during this era. Under the leadership of the renowned surgeon, Joe Vincent Meigs, MD, the first man to be named Chief-of-Staff at the Vincent, the hospital became a leader in the treatment of cancer of the female genital tract. "Dr. Meigs' pioneering effort was in bringing to the pelvis the technical mastery of cancer surgery that had been achieved in other areas of the body," Dr. Richardson said.

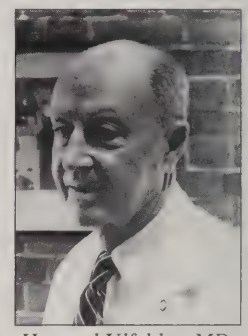
*Joe Vincent Meigs, MD*

Another major achievement in the fight against cancer in women occurred in 1941. That year the Vincent team of Maurice Fremont-Smith, MD, an internist, and Ruth M. Graham, Director of the Vincent's Cytology Laboratory, instituted a method for detecting early vaginal cancer using the Pap smear test.

The Pap smear was originated by George N. Papanicolaou, MD, of Cornell University and New York Hospital. But the subsequent work done by the Vincent team on evaluating and diagnosing changes in the vaginal smear is credited with hastening the acceptance of the early cancer detection procedure by the medical community. In 1971, Howard Ulfelder, MD, Dr. Meigs' successor and protege, published along with Arthur L. Herbst, MD, and David Poskanzer, MD, the results of their study that linked diethylstilbestrol (DES), a drug taken by pregnant women to prevent miscarriages, with the occurrence years later of vaginal and cervical cancer in their female offspring. As a result of the research, the U.S. Food and Drug Administration in 1971 banned the use of DES.

*Maryellen Boutin, RN, a nurse on Ellison 16, the Vincent Gynecology Unit.*

Arlan Fuller, MD, the current Director of the Vincent Gynecology Oncology Division and an outstanding surgeon, continues with the members of his division to maintain the standard of excellence in patient care and research established by Drs. Meigs and Ulfelder.



*Howard Ulfelder, MD*

But the achievements of the Vincent have not been limited to malignancy. In the 1940s Dr. Meigs had also become keenly interested in endometriosis, a noncancerous disease in which the lining of the uterus (endometrium) becomes implanted outside the womb, causing pain and infertility. Dr. Meigs, and later, Dr. Ulfelder, developed several surgical advances to treat this condition. Their work also led to the formation of the Vincent Hospital infertility unit. In collaboration with the Reproductive Endocrinology Unit in the MGH Department of Medicine, the Vincent has become a worldwide center for the study and treatment of infertility in both sexes.

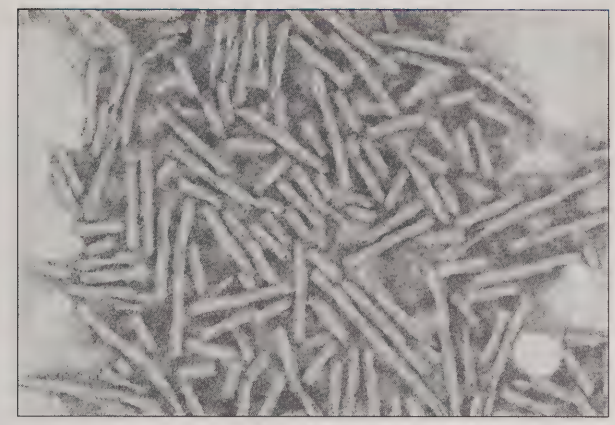
*Arlan Fuller, MD*

During the 1970s a new kind of revolution began at the Vincent — the era of specialization.

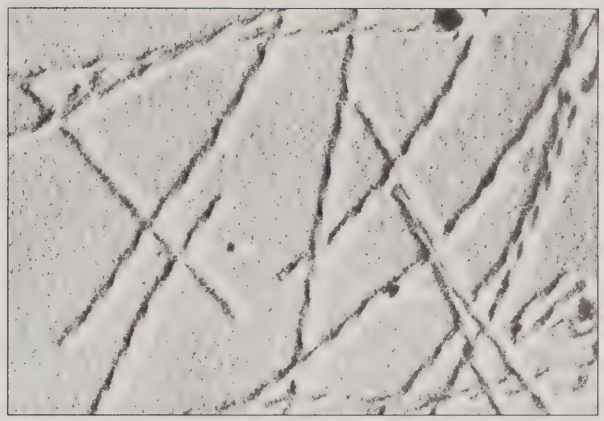
"Although specialization as we know it has been a fairly recent phenomenon, the hospital has always been one of the leaders in treating the diseases of women," Dr. Schiff said. "From its beginning the Vincent has been unique. We not only want to provide state-of-the-art care with compassion and sensitivity, but we wish through our training to be certain that the next generation of women patients continues to receive the same high standard of care." ■

# *Mistake Leads to an Important Study*

## *Could the double helical bovine pancreatic thread protein and the Alzheimer's paired helical filament protein be one and the same?*



*In cows a protein called PTP (Pancreatic Thread Protein) is made up of two threads twisted around one another and coiled up like a tiny spring.*



*Among the many proteins found in man is an unidentified protein in the form of double helical thread-like tangles in Alzheimer's disease.*

***"I knew in my soul they had to be different. They just happened to look like each other. But that was enough reason to go look. Intuition is often more important in science than logic."***

Jerome Gross, MD
MGH Biologist

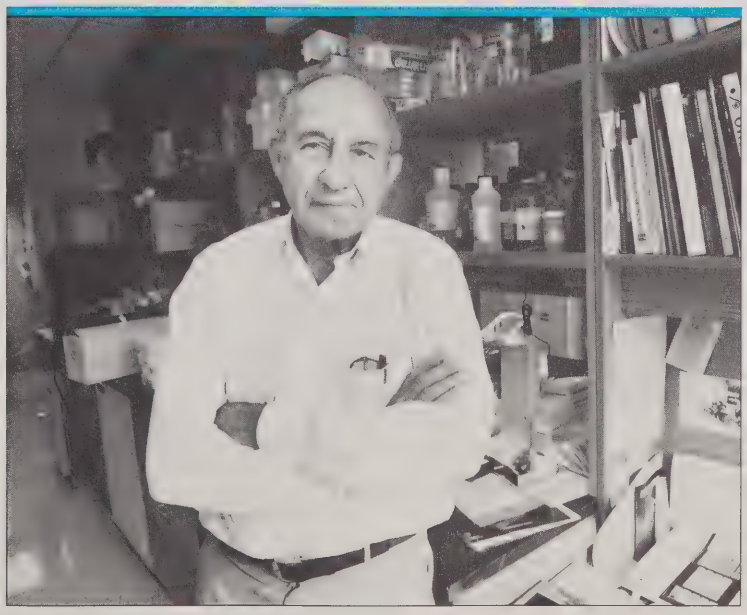
"JUST on the outside chance," Jerome Gross, MD, told his colleagues, "Let's go look for it."

What Dr. Gross, an MGH biologist, was "looking" for was not logical.

In cows Dr. Gross had discovered under the electron microscope that a pancreas-produced protein he called PTP (Pancreatic Thread Protein) was made up of two threads twisted around one another and coiled up like a tiny spring.

In the subsequent search for other proteins which could form double helices (spirals) he recalled the paired helical thread-like tangles that criss-cross damaged nerve cells in Alzheimer's disease.

Could the double helical bovine pancreatic thread protein and the Alzheimer's paired helical filament protein be one and the same? Dr. Gross wanted to look and see even though he knew in humans, PTP had only one thread, not two.



"I knew in my soul they had to be different," he said. "Nevertheless, I couldn't get the structural similarity between the bovine PTP and the paired helical filaments of Alzheimer's brains out of my mind.

"I knew they couldn't be the same. They just happened to look like each other. But that was enough reason to go look. In science intuition is often more important than logic."

Look he did, and lo and behold, as Dr. Gross likes to say, he and his colleagues did find a form of PTP in the brain lesions of Alzheimer's patients.

But not for the reason Dr. Gross thought. Scientists still do not know the identity of the protein associated with the double helical structures in Alzheimer's brains. But Dr. Gross and his colleagues now know it is probably not the pancreatic thread protein.

But a form of PTP turned out to be present in Alzheimer's lesions anyhow.
*(Concluded on Page 8)*

## —Mistake

*(Concluded from Page 7)*

"I was right for the wrong reason."

It is not the first time that Dr. Gross has been both right and wrong about PTP.

The story of PTP began more than 40 years ago with a young investigator who set out to study elastic tissue and got sidetracked.

Along the way there have been many twists and turns, false stops and starts, surprises, disappointments, and always a great sense of adventure.

"I think the most interesting things that we find are not always those that we set out to look for," Dr. Gross said. "Being wrong is not all bad. In fact we frequently get the right answers for the wrong reasons."

In 1949, however, Dr. Gross got the wrong answer for the wrong reason. A second-year research associate at the Massachusetts Institute of Technology, he made a startling discovery about elastin, the rubbery substance that gives elasticity to the tissues. At that time little was known about the structure of elastin. Dr. Gross wanted to study the substance under the electron microscope. But first he had to break it into smaller components.

Treating the elastin with an enzyme (biological catalyst) called trypsin, Dr. Gross put the elastin under the electron microscope and saw what looked like double helical filaments coming out of the elastic fibers. "So the model I drew was a substance made up of double helical filaments like little springs held under compression by an amorphous matrix [shapeless form]. The fibers, which are capable of long-range elasticity, were supposedly broken down by the trypsin, which released these little 'springs.'"

Considered an important advance in the scientific community's understanding of elastin, the finding was published within six weeks in the *Journal of Experimental Medicine*.

Then the roof fell in. Dr. Gross discovered that the trypsin, advertised as "three times crystallized" (highly purified), had been contaminated.

"I could have taken that beautiful pure trypsin and put it with iron filings and gotten the same answer," he said. "The double helical filaments were in the trypsin."

*PTP in humans is a single strand.*

The hunt for the contaminant and what turned out to be a continuing interest was on. Pirating time away from his primary work — collagen and self assembly mechanisms (how molecules assemble complex structures) — and from his new bride — "My wife didn't see me for God knows how long" — Dr. Gross isolated the double helical contaminant from the trypsin and from the bovine and human pancreas. And the more he studied it, the more intrigued he became. "There was nothing like it. I could not find any information about it in the sequence banks in Washington where you have all the information about amino acid sequences of proteins. It looked like a unique protein."

Work on the protein — still unnamed — heated up in 1981 when Dr. Gross and his colleagues, using several highly specific antibodies, began to localize the protein in the human pancreas. The investigators found it was present in huge amounts in the pancreatic fluid. "It was secreted into the pancreatic fluid in a higher concentration than any other protein there," Dr. Gross said.

By now Dr. Gross, who had early on published a retraction and correction to his original paper, had named the double helical protein PTP — pancreatic thread protein. "I wanted to give it a name that would describe it since I didn't have a function for it. I didn't know what to call it. One of my friends in the lab suggested, 'Garbagon.' We had a good laugh about that. He thought I was wasting my time on it."

Dr. Gross and his colleagues still do not know anything about the function of PTP or the form of it that is found in Alzheimer's disease. "But we're going to find out," he says.

And this, Dr. Gross said, is the moral and the ultimate lesson of this twisted tale.

"People make mistakes all the time, but if you are working on a good problem you just don't walk away from a mistake," he said.

"Basic science is intrinsically risky. Mistakes and failures are common, expected, and should teach us. They often lead to more important directions than do our predictable successes." ■

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# MGH Approved to Do Human Islet Transplants

UNDER THE MICROSCOPE islet cells look exactly like one would expect — small islands of tissue floating in a sea of contrasting cells.

The pancreas contains about a million and a half of these little islands. Inside each islet, hundreds of cells called beta cells pump out the insulin necessary for the proper metabolism of carbohydrates.

In diabetes the pancreatic islet cells are either destroyed by the body's own immune system (Type I diabetes) or begin to wear out and die as a person ages and gains weight (Type II).

"For years people have been saying, 'Wouldn't it be great if we could transplant healthy islet cells into a diabetic patient?'" said Denise Faustman, MD, PhD, Director of the Immunobiology Laboratory in the MGH Diabetes Unit. "Sure it's a great idea. But technically it just hasn't been feasible to get the islets out of the pancreas."

Fifteen years of laboratory research appears to have finally yielded a possible solution. Dr. Faustman is now successfully isolating islet cells. Hugh Auchincloss, MD, Chief of Pancreas Transplantation at the MGH, with the collaboration of Dr. Faustman, David Nathan, MD, Director of the MGH Diabetes Research Center, and Joseph Avruch, MD, Chief of the MGH Diabetes Unit, has permission to transplant the islets into Type I diabetic patients. Dr. Nathan is the Principal Investigator of the trial, Dr. Faustman has led the basic research, and Dr. Avruch is the Senior Investigator.

The MGH is one of only a handful of institutions in the country and the only hospital in the northeast conducting or poised to conduct such highly experimental human islet transplantations.

The technical challenge of locating and isolating a million and a half islet cells scattered throughout an organ has been enormous. Despite their number, islet cells make up less than one percent — about a tablespoonful — of the pancreas.

Compounding the challenge is the nature

*(Continued on Page 4)*

## INSIDE

*New Depression Drug*
*See Page 2*

*First Nutrition Chair*
*See Page 7*

## *Children Take Lead in New Speech Pathology Approach*

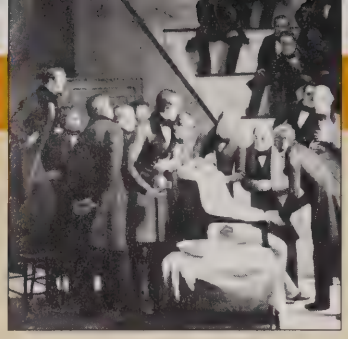
MICHAEL B. WAS 19 months old when speech pathologist Michael D. Smith, PhD, first met him. Born prematurely, Michael B. was dealt a heavy load. He spent his first 42 days in the Intensive Care Unit suffering from respiratory distress syndrome. He encountered cerebral palsy and hydrocephalus (an accumulation of fluid in his skull). At 10 months a developmental evaluation rated him severely mentally retarded. When he vocalized he did not babble.

After spending about five weeks observing Michael at 19 months of age, Dr. Smith found him to be alert, responsive, and with what he felt was

*(Concluded on Page 6)*

*Deborah Proia, a student in the Speech Pathology Graduate Program at the Institute of Health Professions, draws three-year-old Clarissa Rigaud of Lawrence, Mass., into conversation by helping her make an avocado salad.*

EDITORIAL



## Exciting Times for Diabetes Research

THESE ARE EXCITING TIMES for researchers in diabetes.

For diabetics themselves, the next decade could turn out to be the most important since the 1920s when Banting and Best discovered insulin. Insulin, of course, proved to be life-saving for millions of severe diabetics. Even insulin, however, did little to save patients from the ravages of a variety of complications.

As a page 1 article in this issue points out, complications like blood vessel disease and blindness arise from years of inability to regulate the flow of artificially administered insulin the way nature does. Implanting insulin pumps does not seem to be the answer either. And pancreas transplantation brings with it the need for a lifetime of potent drugs to prevent rejection.

Now come investigators who are experimenting with transplants of islet cells from the pancreas. Thanks to a few researchers like the MGH's Denise Faustman, hundreds of thousands of islet cells can be taken from a single pancreas and transplanted to an insulin-dependent diabetic.

Dr. Faustman is working on two major advances that, if successful, could revolutionize diabetes treatment. The first is to learn how to make a human accept islets from an animal like the pig. To achieve this would be to solve the extreme shortage problem that limits the ability to transplant the human pancreas. That step forward would, however, still leave the diabetic dependent on drugs. The downside is that these same drugs so weaken the immune system that the patient is at the mercy of infections.

Step two sounds like a miracle. It would mean getting the human body to accept the pig islet cells ***without*** drugs to suppress the immune system. Nevertheless, Dr. Faustman has already gotten mice to accept human islet cells without medication. She achieved this by devising an elegant way to hide the islet cells from the mouse immune cells which would otherwise attack anything human. As astounding as that feat is, it has so far defied her attempts to use it to hide the human islet cells from the immune cells of the pig, a step intermediate to transplanting pig islet cells to humans. But Dr. Faustman remains optimistic. Should she one day succeed in getting the unmedicated human to accept pig islet cells, science will have cured diabetes.

# *Depression Drug Subject of New Patient Trial*

MGH PSYCHIATRISTS are testing the effectiveness of a new medication in patients with two common forms of depression not widely known by the general public.

On December 31, 1991, the U.S. Food and Drug Administration gave final approval to the drug sertraline (to be sold under the brand name Zoloft) for treating depression.

The MGH is one of five centers participating in a nationwide patient trial to test the drug in two particular types of depression.

"We're trying to characterize subtypes of depression that may be more responsive to one type of antidepressant over another so that we can pick medications that are more likely to be effective," said Jerrold F. Rosenbaum, MD, Chief of the MGH Clinical Psychopharmacology Unit.

Psychiatrists have identified several "subtypes" of depression. The two being studied in this trial are atypical depression and dysthymia.

Atypical depression is one of the most common forms. An estimated 12 to 15 percent of the population suffers a major depression at some time in their lives. About half of the patients treated for depression at an outpatient clinic suffer from the atypical kind.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PHOTOGRAPHS: Pages 1, 8, Linda Goodspeed; Pages 4, 5, Joshua Touster; Islets Page 5, Courtesy of Dr. Faustman; Page 6, Courtesy of Dr. Smith; Page 7, Courtesy of Dr. Walker.

Major depression is characterized by nine symptoms (see chart).

Atypical depression meets all of the criteria for major depression but has several unique characteristics, including overeating and oversleeping.

"Rather than the traditional symptoms of depression — having trouble falling asleep and having trouble staying asleep, insomnia, waking up early in the morning, and loss of appetite — people with atypical depression tend to oversleep and overeat when they're depressed," Dr. Rosenbaum said.

Another distinguishing feature of this condition is a feeling of fatigue or loss of energy that is often experienced as a heavy leaden feeling in a person's limbs — sometimes called "leaden paralysis."

But the hallmark of the disorder is reactivity of moods. For example people with atypical depression tend to be extremely rejection sensitive. "When something happens that's adverse, these people not only feel bad as anybody would, but they also become completely devastated and dysfunctional," Dr. Rosenbaum said. "They might take to their bed, pull the sheets over their head, leave the room dark.

"In some ways they're people whose moods are more affected by adversity. When adverse events occur they're more likely to feel bad and more intensively bad. Conversely, they can transiently feel cheered by positive events."

Dysthymia is a more subtle and less common form of depression. A person can have a diagnosis of dysthymia by having just two symptoms of major depression in addition to a depressed mood. The difference is these symptoms must be present for two years or more — and five years or more to qualify for the MGH study.

"An estimated three percent of the population meet the criteria for dysthymia, but many of such patients also have other conditions — an anxiety disorder or a medical illness," Dr. Rosenbaum said. "Pure dysthymia without any other condition is relatively rare."

The MGH trial will be a 12-week "double blind" study of 45 atypical patients and 21 dysthymia patients. Participants will be randomly assigned to receive either imipramine (a drug commonly used to treat depression), sertraline, or a placebo (sugar tablet).

Psychiatrists believe sertraline will be particularly effective in the treatment of atypical depression because of the drug's chemical makeup.

Atypical depression is thought to be caused by a poorly regulated serotonin system, one of the neurotransmitter systems (chemical messenger systems) in the brain.

"Sertraline is one of the new generation antidepressants that's very selective for regulating the serotonin system," Dr. Rosenbaum said. "It is thought to re-regulate what is presumed to be a disregulated serotonin system."

Sertraline is part of the same class of drugs as fluoxetine (sold under the brand name Prozac), a fairly recently approved drug that has already become a standard therapy for treating depression and several other conditions, including eating disorders, obsessive-compulsive disorders, and anxiety disorders. Like sertraline, fluoxetine selectively affects the serotonin system. "There are subtle differences between the two drugs, although in general they seem to be more alike than different," Dr. Rosenbaum said. "Sertraline is somewhat more selective than fluoxetine for affecting serotonins. Further, sertraline has a more potent effect on dopamine, another neurotransmitter. But we don't know whether that confers any real advantages or not.

"Although we do not have the extensive experience with sertraline as we do with fluoxetine, some have suggested it may cause fewer side effects, such as agitation, and be a little better tolerated," Dr. Rosenbaum said.

While fluoxetine has achieved wide patient use in a relatively short time, Dr. Rosenbaum said the drug has not been systematically tested to determine if it is more or less effective in treating different subtypes of depression.

In addition to the drug study, MGH researchers have added other components to the patient trial. One "add on" will test the effectiveness of cognitive therapy in treating these two forms of depression.

"One of the issues we want to study is whether these conditions can be treated by nonpharmacologic means," said Maurizio Fava, MD, Director of Depression Research at the MGH. "Cognitive therapy is one form of psychotherapy that has been studied and shown to be effective in milder forms of depression."

So in addition to the drugs and placebo, patients in the trial will also be randomized to receive cognitive therapy.

"It'll give us a chance to have a kind of horse race between cognitive therapy and drug treatment with a placebo control built in," Dr. Rosenbaum said.

Another add-on to the MGH study will measure the prevalence of "anger attacks" and their response to the drug and cognitive therapy treatments.

Anger attacks are intense eruptions of anger. "We've found these were very common in people suffering from these types of depression," Dr. Rosenbaum said. "Over 40 percent of the people in our program have had these anger attacks."

Dr. Fava has designed a questionnaire to test participants before, during, and after the treatments. The questionnaire measures the presence of anger attacks and whether they respond to treatment.

The FDA's recent approval of sertraline means that the drug has already been shown to be effective for the treatment of depression in general.

"The question now is, 'Is it more effective than older drugs for these subtypes of depression?'" Dr. Rosenbaum said. "That's what we want to determine in this study. This is especially important because of the large number of people with these problems." ■

## *The Symptoms of Major Depression, Atypical Depression, and Dysthymia*

### MAJOR DEPRESSION

**A depressed mood and/or loss of interest in normal activities, plus 4 of the following***

- Inability to experience pleasure
- Sleep dysfunction
- Feeling excessive guilt
- Loss of energy, poor concentration
- Appetite change
- Psychic activity change, either retardation or agitation
- Suicidal thoughts, feelings, behavior

(*Must have symptoms for 2 weeks or more)

### ATYPICAL DEPRESSION

- Oversleep
- Overeat
- "Leaden paralysis"
- Extreme rejection sensitivity

### DYSTHYMIA

**Depressed mood plus 2 of the following****

- Appetite change
- Sleep change
- Low energy or fatigue
- Low self-esteem
- Poor concentration, difficulty making decisions
- Feeling of hopelessness

(** Must have symptoms for 2 years or more)

# — MGH Approved to Do Human Islet Transplants

*(Continued from Page 1)*

of the pancreas itself. The other 99 percent of the organ is made up of outwardly secreting (exocrine) cells which produce enzymes necessary for food digestion.

"For years the pancreas has been known as the 'no touch' organ because of these exocrine cells," Dr. Faustman said. "If one little exocrine cell necroses [dies], it releases its digestive enzymes which turn around and digest its neighbors. This releases the digestive enzymes in the neighbor cells. They digest the next cell, and on, and on, and on. It's like a chain reaction."

For several years, however, surgeons have successfully transplanted a whole pancreas despite the risk of setting off this chain reaction.

The MGH began transplanting whole pancreases into Type I diabetic patients in 1986 *(MGH News, March 1987)*. Pancreas transplants are now performed at about 50 centers nationwide. The MGH, with 36 transplants, is rated among the top with a one-year, 86 percent graft survival rate.

Although a pancreas transplant cures diabetes by eliminating the need for daily insulin injections, it has several disadvantages.

"We took away insulin, but we were adding the risk of major surgery and major immunosuppression," Dr. Auchincloss said. "It was not in ordinary circumstances a good tradeoff. We felt it was not the final answer to diabetes."

Because of the risks associated with the operation and with the powerful immunosuppressant drugs needed to prevent rejection, the procedure was carried out only on patients needing immunosuppression and major surgery because of a simultaneous kidney transplant.

"By definition the people in whom we were performing the pancreas transplants already had renal failure and other very far advanced complications from their diabetes," Dr. Nathan said. "The chances that we could reverse the complications at this late stage were pretty slim.

"But if we were to do the operation in children who didn't have these serious complications, you're talking about exposing them to major surgery and major immunosuppression. So trying to decide the appropriate timing for this operation was very difficult. Whole pancreas transplantation is a great technical procedure that can actually cure people's diabetes metabolically, but it can't be implemented in children."

Because of these concerns, the MGH group for the last year has switched much of its clinical and basic research efforts from pancreas transplants to islet transplantation.

"We wanted something that technically was not such a huge operation and that didn't need immunosuppression," Dr. Auchincloss said. "Islets may potentially fit the bill on both counts."

In contrast to a whole organ transplant, the actual surgery to transplant a tablespoonful of islet cells is simple. The islets are simply injected into the liver through the umbilical vein. By itself the procedure could be done under a local anesthetic at the bedside.

Any foreign tissue can be rejected, but researchers believe they can overcome the problem in islet cells. From animal experiments in mice scientists have discovered that islet cells are less easily rejected than a whole organ. "But that doesn't mean they're going to survive unless you do

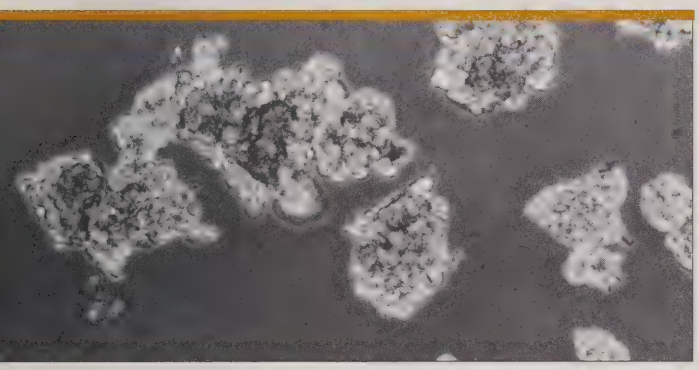
something special to them to prevent them from being rejected," Dr. Faustman said.

Currently the protocol approved by the MGH Subcommittee for Human Studies for the islet cell trial is much the same as the pancreas transplant protocol. Initially the islets are to be transplanted only into Type I diabetics who are already receiving or about to receive immunosuppression because of a kidney transplant.

Ultimately the MGH group hopes work being done in Dr. Faustman's laboratory will enable them to transplant the islet cells without immunosuppression.

"The basic concept is you modify the graft [transplanted cells], not the recipient," Dr. Faustman said. "All immunosuppressant drugs are based on the concept of modifying the recipient. We're approaching it from the other end."

In order for rejection to occur, lymphocytes (white blood cells which cause an immune reaction) must "stick" to the foreign tissue. "What we have attempted to do in animal studies is modify the graft so that the molecules the lymphocytes stick to are invisible," Dr. Faustman said. "The lymphocytes just swim on by the graft. They don't stick to the tissue, which means their T cells don't get revved up, and they don't kill the target."



Dr. Faustman and her colleagues have used her technique to transplant human islet cells into mice. She was able to hide the human islet cells so well that the mice accepted them as their own, and the need for immunosuppressant drugs was avoided. Two hundred days later the cells show no signs of rejection. Published in *Science*, her results received worldwide attention.

That kind of drug-free islet transplantation is a long way off in this MGH trial. Many other questions must be answered first. For instance, how many islet cells does a diabetic need? Researchers want to answer these questions before tackling the more ticklish issue of tolerance.

***Left:*** *Denise Faustman, MD, PhD, and Hugh Auchincloss, MD*
***Above:*** *Islet cells*

The best laboratory techniques currently yield only about one-third of the available islet cells from a single pancreas. Yet each year fewer than 3,000 pancreases are donated. By the year 2010, doctors estimate 10 percent of the U.S. population will have diabetes. Although most of the diabetic patients have the older age, Type II diabetes, there will be a large imbalance between the number of Type I diabetics and the number of pancreases available. Because of this imbalance, most believe the future of islet transplantation rests with xenografts — cross species transplants *(MGH News, March 1990)*.

"The logistics say that human donation is just not feasible," Dr. Faustman said. "So you have to think about alternative sources of donor tissue. And the alternative source that makes the most sense is to use an animal that's already part of the food chain, and that would be pig islets."

Type I, or juvenile-onset diabetes, afflicts only about 10 percent of all diabetics. In Type I diabetes, a patient's own immune system destroys all the islet cells.

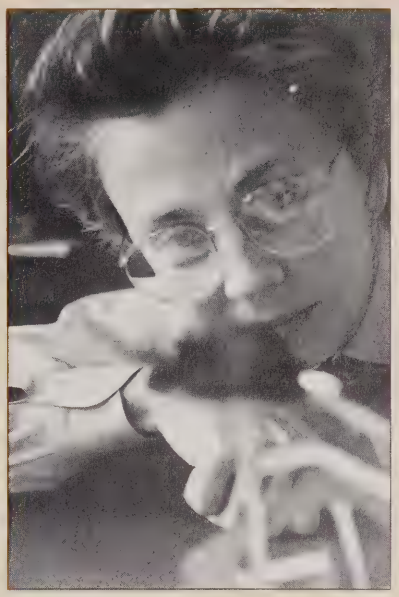
Although only Type I diabetics will be treated in the current MGH islet transplantation trial, the MGH group believes the procedure may one day be extended to treat Type II diabetics as well.

"The issues of Type II diabetes are different than the issues of Type I," Dr. Faustman said. "But if you have Type II diabetes for many years, you also end up on insulin injections with decreased functional islets. In that case there's some hope, although very early, suggesting that islets may work in Type II diabetics as well as Type I. But our primary focus is Type I diabetes."

The MGH group will perform as many procedures as funding permits and early results encourage. The procedure, which costs upwards of $50,000, is not reimbursed by insurance carriers and thus limits the number of patients able to be treated.

"We're taking a step-by-step approach in our trial," Dr. Nathan said. "Phase I will include patients who either have a kidney transplant already or are about to receive one. After that we'll start looking for people with less advanced complications as we move into the next phase and begin to back off the immunosuppression. And finally we'll start treating people at the onset of their disease.

"We hope this is all possible within a 10-year window of being able to cure diabetes." ■



*Denise Faustman, MD, PhD*

## *Defining 'Cure'*

WILL islet transplants "cure" diabetes? It depends on your definition of cure — and from what direction you approach the disease.

"To me, cured of diabetes means you never get diabetes," said Denise Faustman, MD, PhD, Director of the Immunobiology Laboratory in the MGH Diabetes Unit. "To most patients, cured of diabetes means they don't have to take their insulin injections anymore.

"So there's the basic science definition of cure which means that you prevent the disease from ever happening. And then there's the patient definition of cure my disease so I don't have to take insulin anymore.

"In the patient sense, islet transplants can cure diabetes because they eliminate insulin.

"Does that mean that this is the way we'll be treating diabetes 100 years from now? Maybe some patients will get islet transplants. But more likely, with additional research, we'll be able to stop the disease from ever happening in the first place.

"But we're a long way off from that definition of cure because we still don't understand well enough how the disease normally occurs to intervene in a specific way. The day when we'll be able to cure diabetes in every sense of the word is still many, many years away." ■

# — Children Take Lead in New Speech Pathology Approach

*(Concluded from Page 1)*

more potential than earlier assessments had given him.

"Michael had been receiving some very traditional pre-speech therapy," Dr. Smith said. "Twice a week he would go to a speech therapist for half hour sessions during which time the therapist would try to get him to vocalize and say his sounds right.

"I basically approached it from an interactive standpoint."

Michael loved trucks and trains and vocalized when playing with them. Working with Michael's family, Dr. Smith set up several "routines" in Michael's home involving trucks and trains. The "routines" were a series of related events — sometimes called "scripting" — designed to elicit spontaneous conversations with Michael.

*Six-year-old Michael B., who was born with several complications of premature birth, is now working with his peers in a public school classroom. His IQ, once tested at under 40, is now rated normal.*

"We'd take one of his trains and push it down the tracks talking about it, making 'choo choo' sounds, and blowing the horn. Then we'd take one of his trucks and drive it down the road. The truck would have to stop for the train. And we'd talk about that, using appropriate language. Michael's language began to sound more and more intelligible."

The "routines" were extended to include Michael's twin brother. Later when Michael entered a preschool, the routines were expanded to include his preschool teacher and physical and occupational therapists.

"I essentially participated in drafting a comprehensive educational program for him, including the development of social skills and language skills," Dr. Smith said. "As his language became more intelligible he began blossoming."

Michael, who is now six, is currently in a regular public school classroom with his peers. His IQ, once tested at under 40, is now rated normal.

Michael B. is an example of a growing trend in speech pathology toward the treatment of language problems among neurologically involved infant toddlers. Just because a medically fragile child's use of language sounds odd or abnormal does not mean it is functionally disordered.

"It's just different," said Dr. Smith, a professor in the new Speech Pathology Graduate Program at the Institute of Health Professions, the educational affiliate of the MGH. "It's behavior that's far enough down a performance continuum that it sounds odd. But however odd it may sound, it is advantageous to assume that there is some logic to that language.

"And as speech-language pathologists, our task is to find out as much as we can about the child's language and then to nurture that behavior closer to what we consider to be acceptable and intelligible performance.

"But we have to do it within the framework of that particular linguistic system — that child's world. We have to do our work from within the system and not from outside the system."

Dr. Smith, a PhD-trained linguist who spent the last 10 years as Clinical Director of the Graduate Program in Speech-Language Pathology at Western Carolina University outside Ashville, N.C., is bringing more than just theory to the first-ever class of speech pathology students at the I.H.P. In fact Dr. Smith believes traditional graduate education has relied too much on isolated "classroom" theory and not enough on what he calls "field worker" mentality.

"We have to take more of a field work approach to the practice of speech-language pathology," he tells his students. "In a sense we have to behave more like anthropological linguists." He cited Michael B., whom he treated while in North Carolina, as an example.

The "field worker" approach to child language disorders that Dr. Smith is bringing to the new I.H.P. Speech Pathology Program is not unique. Since about the early 80s, he said, the field has been slowly moving in this direction.

Instead of pulling a child with a language disorder out of his environment for diagnosis and treatment, the speech-language pathologist evaluates and works with the child more in his natural environment.

"In the past we essentially applied the logic of deficit ledgers to child language disorders and tried to fix problems," Dr. Smith said. "In this model you diagnose an individual, you find out what the problem is, and you fix the problem — sort of a cut-and-paste operation.

"We're now looking at these children more from the perspective of social psychology and treating children as active participants in the clinical process.

"Here the child takes the lead. In the old model the speech pathologist took the lead," Dr. Smith said. "Today we're the followers. We've stopped viewing ourselves as the primary agents of change. Along with the child, we're now agents of integrated development."

In the case of Michael B., the child's own love of trucks and trains helped set the agenda for the therapy sessions.

Dr. Smith believes that extended observation and in-depth diagnosis are the keys to a successful developmental conversational approach to child speech therapy.

"It may be the case with someone like Michael B., for example, that it will take weeks and multiple sessions to figure out the child's system. We then write a descriptive grammar for that child, all the time taking the opportunity to work within the child's system and not outside of it."

The strong neurolinguistic orientation of the I.H.P. Speech Pathology Program particularly attracted Dr. Smith to the MGH.

"What it means is that we're working with the mind. We're assuming that young children — however unintelligible their speech might at first sound — come with a developmental agenda and because of this there's a system and there's potential, neurologically based potential.

"Our job is to engage that individual in the process of developing that potential." ■

# Dr. Allan Walker Named to First Nutrition Chair

AT WHAT AGE should children be given low-saturated fat in their diets? Begin eating fiber? Have their cholesterol checked?

"High cholesterol levels in adults can lead to hypertension, stroke, or heart attack," said W. Allan Walker, MD, Chief of the Combined Program in Pediatric Gastroenterology and Nutrition at the MGH and Children's Hospital. "But we don't know at what point we should start worrying about cholesterol levels in children. What is the norm for a one-year-old? For a five-year-old?

"We're now starting to look at diet in a more prospective fashion. As we start dietary intervention and prevention earlier on, I believe we'll begin to see a decrease in certain diseases," Dr. Walker said.

Translating important research on cholesterol, fiber, breast milk, vitamins, trace elements, and other nutritional subjects to the diets of children is Dr. Walker's primary goal as the Conrad Taff Professor of Nutrition and Pediatrics at Harvard Medical School. The Taff Chair, the first at Harvard in nutrition, will be permanently located in the Children's Service at the MGH. It establishes nutrition for the first time as a separate discipline within the Harvard Medical School community.

"We want to develop nutrition as a specialty," Dr. Walker said. "Right now there are individual lectures in nutrition at Harvard, but the students don't take away from them the translation of how you deal with nutritional problems in the practice of medicine."

To carry out this educational mandate Dr. Walker is establishing a Conrad Taff Lectureship at Harvard, visiting professorships at the MGH and at Children's Hospital, training programs in nutrition for physicians in medicine, surgery, pediatrics, and other disciplines, and several periodicals. As physicians become more informed about current research developments in nutrition, their patients will also become better informed.

"We want to provide both lay people and physicians in practice with updated information about nutritional management and breakthroughs in research that can help explain how best to feed an infant," Dr. Walker said.

As part of this effort, Dr. Walker and the MGH successfully competed for a National Institutes of Health "center" grant. The Center in Nutrition, 1 of 11 NIH-funded nutrition centers in the country, will pull together investigators in diabetes, pathology, preventive medicine, cardiology, pediatrics, and other specialties to work on nutritional research. "It's a cross-disciplinary approach to looking at nutritional problems from a basic as well as an applied perspective," Dr. Walker said.

Considerable research in recent years has focused on the role of improved nutrition in the ability of the immune system to ward off infection. Much of this research, however, and the recommendations that have followed, have been directed at adults.

"Now we're beginning to take into pediatrics important nutritional factors that we've been aware of in adult diets," Dr. Walker said.

Cholesterol is one example. Vitamins are another. "There's good evidence to suggest that vitamins can prevent the production of certain carcinogens [cancers], or that certain defense mechanisms are vitamin dependent," Dr. Walker said. "But most of the work that has been done on vitamins has been done in adults. One of the roles of the pediatric investigator is to determine what vitamins and nutrients are appropriate for an infant."

Recent findings, for example, reveal that breast-fed infants should be supplemented

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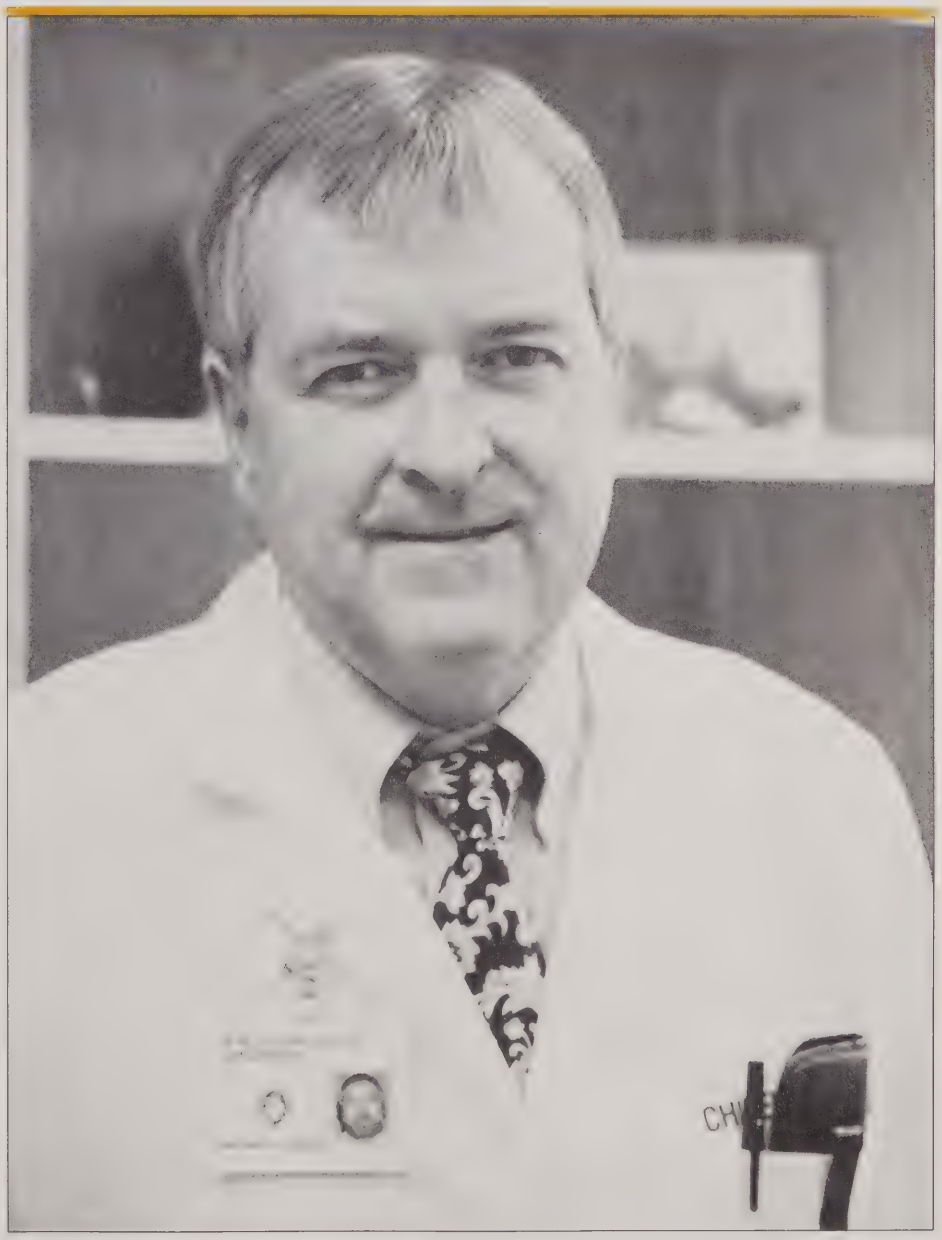

*W. Allan Walker, MD*

## —Nutrition Chair

*(Concluded from Page 7)*

with iron after the first four months. "Even though there's a small amount of iron in breast milk, it's not enough to supply an infant's needs after the first four months," Dr. Walker said.

On the other hand, too much protein, particularly milk protein, in a breast feeding mother's diet — once thought essential for the health of both mother and infant — can cause severe illness in a child.

"Small quantities of that dietary protein can get into breast milk and in some instances can cause a severe colitis, which is an inflammation of the colon, bleeding, and diarrhea in an infant," Dr. Walker said. "If you take the mother off that diet and she continues to breast feed, the baby does well."

The nutritional implications of breast milk, and particularly its role in guarding a newborn against infectious diseases, have been a primary focus of Dr. Walker's own research. He has been particularly interested, for example, in the role breast milk can play in preventing necrotizing enterocolitis (NEC).

A disease primarily of premature infants, NEC is characterized by bloody diarrhea, abdominal distention, and eventual perforation (piercing) of the bowel. It is caused by the inability of the infant's intestines to handle bacteria.

Dr. Walker and his colleagues have found that growth factors in breast milk can prevent bacterial colonization and penetration of the intestines and reverse and guard against NEC *(MGH News, January-February 1989).*

Related to his work on breast milk is Dr. Walker's interest in food allergies in infants. How and why some foods cause certain infants to develop allergic reactions, asthma, eczema, diarrheas, etc. has been a focus of his research efforts.

This summer Dr. Walker will travel to Paris to work in the laboratory of Dr. Daniel Louvard, Chairman of Molecular Biology and Cell Biology at the Pasteur Institute.

Dr. Walker and his colleagues will be attempting to establish a fetal human cell line. From the intestines of therapeutically aborted infants, they will extract cells and then genetically treat them in an effort to keep them alive and functioning indefinitely in the laboratory.

"If we are successful in establishing this fetal cell line, it will be an enormous step forward in helping us to answer some very basic questions about nutrition," Dr. Walker said. "What is it, for instance, in breast milk that causes cells to develop in such a way that they will not allow bacteria to penetrate and cause NEC?

"That's about as far away from what you think of as standard nutrition as you can get. But it can potentially answer some very exciting questions in nutrition that can be applied to what children should or shouldn't eat, what vitamins and nutrients need to be supplemented in their diets, under what circumstances should they be breast fed, and so forth.

"What people think of as good nutrition doesn't necessarily mean appropriate calories, enough protein, or whatever, in their diets. It has to do with trace elements such as zinc and phosphorous, with vitamins and other nutrients.

"I think it's a very exciting time." ■

*Diana Buckley, RN, draws blood from Candace Graham, 9, of Lawrence, Mass., in order to check Candace's cholesterol level. Mrs. Christine Graham gives her daughter emotional support.*

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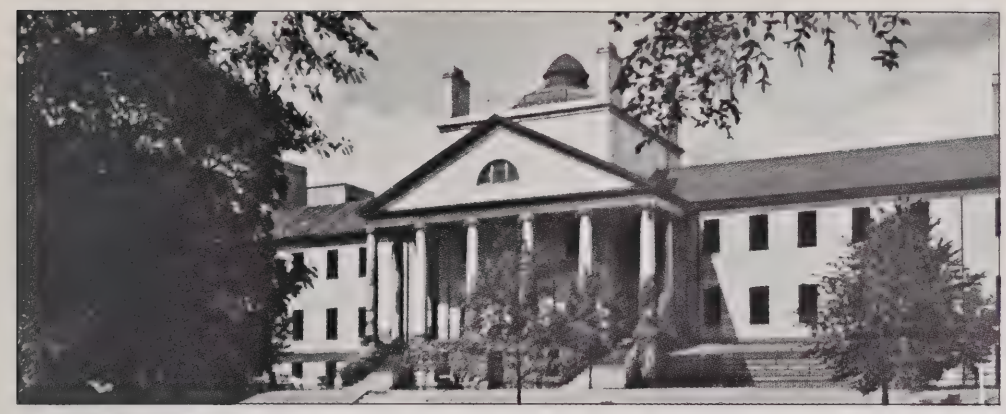

MGH News

Massachusetts General Hospital, Boston, Massachusetts Vol. 51 No. 3 April 1992

# MGH Researcher Looks for More Effective Ways Of Delivering Anticancer Drugs to Their Targets

THE BEST cancer drug in the world is of little use if it fails to reach its target cells inside the tumor. And therein lies the heart of Rakesh K. Jain's work.

Advances in molecular and cellular biology of cancer have led to the genetic characterization of tumors. These advances have also led to the development of various genetically engineered molecules and cells, potentially useful for cancer treatment.

"To realize the clinical potential of these novel agents we need to develop strategies to deliver them to tumor cells in patients," said Dr. Jain, newly named Director of the Edwin L. Steele Laboratory for Tumor Biology, part of the Department of Radiation Oncology and the MGH Cancer Center.

Solid tumors that develop in the breasts, lungs, stomach, and other organs are responsible for most cancer deaths. Many cancer treatments will shrink tumors, but few erase them completely.

"The question we started asking is 'Why is this?'" Dr. Jain said. "The hypothesis we are pursuing is that most of the drugs don't get into the tumor in optimal quantities.

"Since delivery of drugs and nutrients such as oxygen are governed by tumor physiology, we decided to focus our efforts on developing the basic understanding of tumor physiology."

Dr. Jain has been studying tumor

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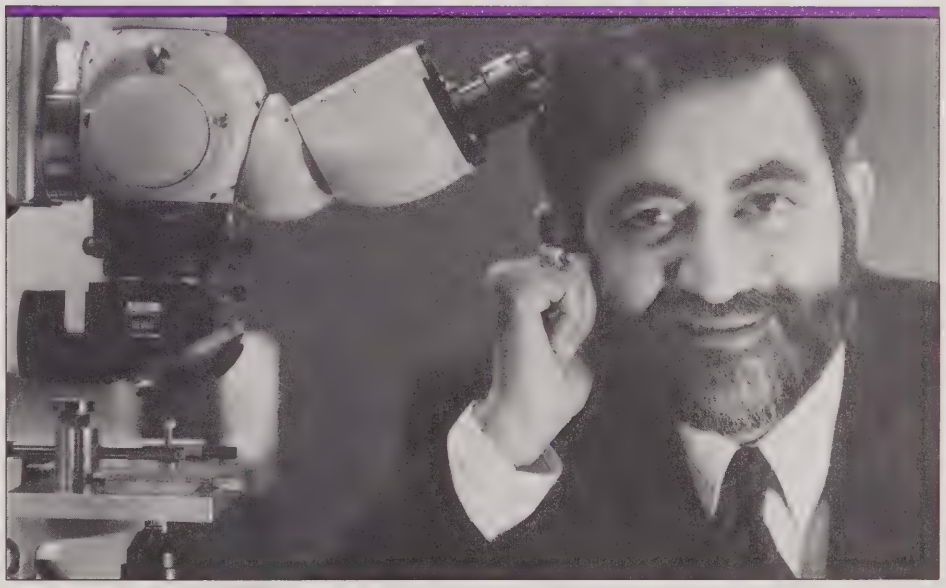

*Rakesh K. Jain, PhD*

## *Safer Blood Supply, Alternative Techniques As Blood Transfusion Service Turns 50*

THE GIFT OF LIFE is no longer the gift of a single life.

It is the gift of three lives.

Blood component therapy — spinning whole blood down into equal parts: red cells, platelets, and plasma — has been the single greatest advance in blood banking and transfusion techniques over the last half century.

But if component therapy has expanded the gift of life, the AIDS epidemic has brought the realization that the gift sometimes comes with strings attached.

"The AIDS epidemic and the heightened awareness about other infectious diseases like hepatitis that can be transmitted through the blood supply has led people to be much more cautious about transfusion therapy," said Christopher Stowell, MD, PhD, Director of the MGH Blood Transfusion Service.

Among the precautions now taken at the MGH and other blood banks to ensure the safety of donated blood are stepped-up screening of donors and more rigorous testing of blood. From four tests a decade ago, technologists now perform nine tests on every unit of blood collected — and soon will perform a tenth test.

"One of the spinoffs of doing tests for other viruses is that you sometimes discover viruses you weren't looking

*(Continued on Page 5)*

INSIDE

***Computer-Aided Diagnosis***
***See Page 7***

# The Red Sea

MGH'S FIRST BLOOD TRANSFUSION took place eight decades ago on July 24, 1912. As a page 6 article points out, by today's standards the procedure was primitive. And a half century ago on April 1, 1942, the MGH opened its Blood Transfusion Service. In the 50 years since, the hospital has transfused an estimated million units of blood components, perhaps enough to transform an ordinary lake into a miniature Red Sea.

Blood transfusions, however, have not only become common but also infinitely safer — despite concern about AIDS. The public is gradually becoming more sophisticated in separating truth from myth about the HIV virus that causes AIDS. By now many people realize, for example, that you can not catch AIDS by donating blood. It is possible, though, to develop AIDS from receiving HIV-tainted blood. Yet nowhere near as possible now as most people believe. In a front page article Dr. Christopher Stowell, Director of the MGH Blood Transfusion Service, puts that in perspective in a manner that demands attention: "More people will be struck by lightning than will get AIDS from a blood transfusion."

Although AIDS attracts the headlines, hepatitis is a more likely, though not common, result of receiving a transfusion. With improved tests and autologous blood techniques, the risk even of a hepatitis-borne blood transfusion has declined precipitously. And is likely to continue its decline.

The 50 years since the MGH opened its blood transfusion service have been remarkable in many other ways as well. Advances, many of them pioneered at the MGH, have also made blood transfusion much more efficient. Poised probably for at least some use in the near future is artificial blood. One day it will probably revolutionize the field more than any other single advance in history. ■

## — Tumors

*(Continued from Page 1)*

physiology and the problem of drug delivery for the last 15 years — not, however, at a medical school or even in a biology laboratory, but in a chemical engineering department. A mathematician by training with a PhD in chemical engineering, Dr. Jain was Director of the Tumor Microcirculation Laboratory at Carnegie Mellon University in Pittsburgh, an institution that does not even have a medical school.

Dr. Jain admits the unusual combination of a chemical engineer doing cancer research caused much skepticism at first. "My first six grant requests were turned down," he laughs. "The funding agencies did not recognize the importance of drug delivery and tumor physiology."

The 41-year-old Indian-born researcher is no longer being ignored — or turned down. Among the many awards he has received for basic research are a Guggenheim Fellowship, a Research Career Development Award from the National Cancer Institute, and a Humboldt Senior Scientist Award. Last September in conjunction with his MGH appointment he was named Andrew Werk Cook Professor of Tumor Biology at Harvard Medical School. He has also been named professor in the division of health sciences and technology at the Massachusetts Institute of Technology. Dual appointments at both universities are not unheard of, but they are unusual and a testament to Dr. Jain's standing in both the medical and chemical engineering fields.

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PHOTOGRAPHS: Page 1, Scott Goldsmith; Page 4, Courtesy of Dr. Rakesh K. Jain (Tumor Illustration); Michael Maskarinec (Rabbit Ear Chamber); H.A. Lehr (Mouse Illustration); Pages 5, 6, From the MGH Archives; Page 6, (Dr. Stowell) Bill McCormack.

Dr. Jain became interested in tumor physiology while studying for his PhD in chemical engineering at the University of Delaware. His advisor, James Wei, PhD, who later became Chairman of the Chemical Engineering Department at MIT and is currently Dean of the School of Engineering and Applied Sciences at Princeton University, invited him to work on a problem that had intrigued Dr. Wei for some time. "He wanted me to find out how much of a drug enters and leaves a tumor," Dr. Jain said. "To me it looked like a very good chemical engineering question. We design a chemical plant by measuring input and output and inferring from that the structure of the plant."

A novice in the life sciences (in high school in India he took Sanskrit to avoid biology), Dr. Jain read a book Dr. Wei gave him on human physiology in one week. At the end of the week he joined Pietro M. Gullino, a renowned pathophysiologist at the National Cancer Institute.

Since then Dr. Jain has been studying the difficult problem of tumor microcirculation, first at the NIH with Dr. Gullino, then for 3 years at Columbia University, and for the last 13 years at Carnegie Mellon. Over the years he and his colleagues have discovered several barriers that make it difficult for cancer drugs to enter a tumor.

A tumor is much more than simply a collection of cancer cells. In fact cancer cells make up only about 50 percent of a tumor. The rest is composed of what scientists call the vasculature and the interstitium.

If a tumor were a jar of marbles, the marbles would be the cancer cells and the spaces in between the marbles would be the interstitial compartment. The vasculature is the tumor's pipeline or blood supply system, bringing nutrients into the tumor and removing waste products. The vasculature makes up about 10 percent of a typical tumor, and the interstitium 40 percent.

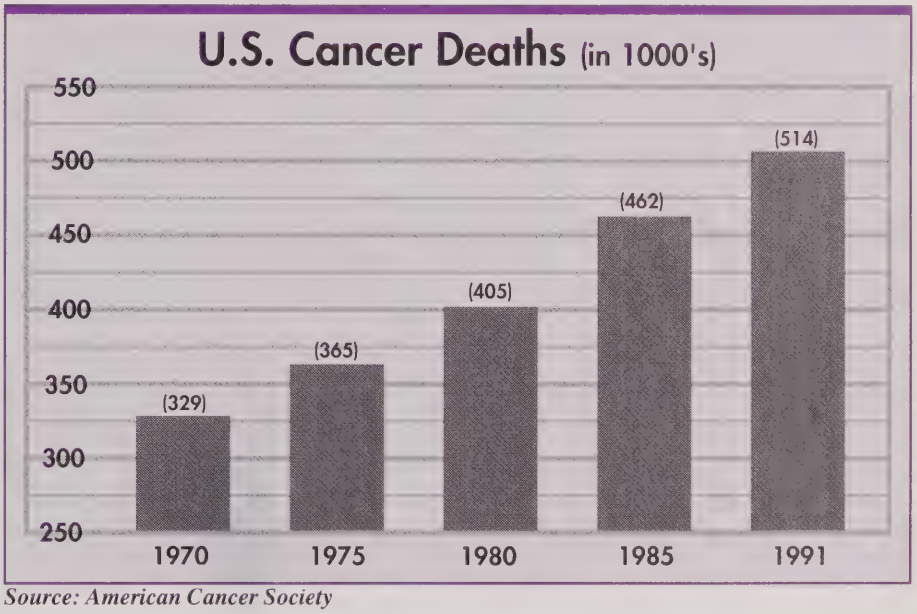
"These two areas have largely been neglected by the cancer community," Dr. Jain said. "They've been focusing on the cancer cells, and there's nothing wrong with that, but somebody has to look at the other half."

Dr. Jain and his team have contributed to the basic understanding of several barriers within these compartments that make it difficult for cancer drugs to reach the cancer cells. First, the blood supply in the tumor is not uniform — some cancer cells receive sufficient blood supply; others do not. Because of this irregular and intermittent circulation, externally introduced molecules must often travel great distances and take many days or even weeks to reach parts of the tumor. This peculiar nature of tumor blood flow also makes certain regions of tumors hypoxic (low oxygen), which is believed to be an important cause of radiation treatment failure.

Second, fluid pressure within the interstitial compartment is elevated.The pressure is high because of: 1) leaky blood vessels; 2) lack of a tissue drainage system; and 3) compression of blood vessels by rapidly growing tumor cells. This elevated pressure makes it difficult for drugs to enter the tumor.

"Any time a large molecule like an antibody tries to get out of the blood vessel, the higher pressure of the tumor slows it down," Dr. Jain said. "You can leave the door to a room open, but if someone is standing in the doorway pushing you out, you can't easily come into the room."

Normal tissue has a pressure of around zero. In tumors Dr. Jain and his colleagues have measured pressures of 40 or 50 millimeters of mercury or more.



*Source: American Cancer Society*

"One of the goals of our research is to try to lower this pressure inside the tumor," Dr. Jain said. In a paper published Dec. 15, 1991, in the journal *Cancer Research,* Dr. Jain reported that he and his colleagues were able to lower tumor hypertension in some women with cervical cancer through the use of fractionated (small doses of) radiation. ***In four of the seven women where tumor pressure decreased, their tumors completely went away.***

"That study has given us a lot of hope," Dr. Jain said.

In addition to his basic research in tumor physiology, Dr. Jain intends to continue those studies here in patients with breast, lung, brain, and cervical cancers, head and neck tumors, and soft tissue cancers.

The opportunity to work with large numbers of cancer patients and collaborate closely with cancer physicians and researchers was one of the main reasons Dr. Jain came to the MGH. Another factor was the opportunity to study human tumors in animals.

These researchers study tumor physiology in two different ways. Both are animal models. In the first model, developed by Dr. Jain's mentor Dr. Gullino, researchers grow in a rat a tumor that has a single artery and a single vein. "In this way we can measure everything going into and coming out of the tumor," Dr. Jain said.

"But it's a black box approach in the sense that we can tell how much of a drug enters the tumor and how much leaves, but we cannot tell what is happening to the drug inside the tumor."

The next step was to develop a transparent tumor. Dr. Jain accomplished this in the ear of a rabbit. "With this model we could visualize the entire tumor and what happened to any drug that entered the tumor," Dr. Jain said. "It gave us an incredible amount of information."

The disadvantage to this model, however, was the inability of scientists to grow human tumors in rabbits. "What we had to do was to grow this kind of tumor in an animal that would accept human tumors," Dr. Jain said.

Enter Herman D. Suit, MD, PhD, Chief of the MGH Department of Radiation Oncology. He has been interested in the mechanisms of failure of radiation therapy to eradicate tumors of certain categories. More specifically his research has focused on the physiologic and metabolic factors which govern radiation response, an area of interest to Dr. Jain as well.

Over the years Dr. Suit has been studying the effects of radiation therapy on human

*(Concluded on Page 4)*

## — Tumors

*(Concluded from Page 3)*

tumors grown in special immunodeficient mice. Dr. Jain now also has access to this colony for his tumor research, making transparent human tumors available for experiments. Dr. Jain credited both Dr. Suit and Dr. Kurt J. Isselbacher, Director of the MGH Cancer Center, for their support of his research efforts.

"Now we are able to follow a human tumor in a live animal in a continuous, noninvasive fashion," Dr. Jain said. "We can actually see various blood-borne agents coming in, where they're going and leaving. We can also monitor various physiologic and metabolic events noninvasively in a live animal. It's exciting."

The MGH is the only institution in the world with all of these animal models available for studying tumor physiology. "It's a wonderful opportunity," Dr. Jain said.

Dr. Jain has put together an extraordinary team of talent. Well known for the loyalty he inspires among his colleagues and for his multidisciplinary approach to basic research, he brought five members of this team with him to the MGH. He has also recruited six research fellows and a graduate student since he has been here. His team includes an immunologist, two chemical engineers, two mechanical engineers, a pathologist, a surgeon, a radiation biologist, a radiation oncologist, and two technicians — one a specialist in cell cultures, and the other a specialist in growing tumors.

"I feel like I am conducting a symphony," Dr. Jain said. "If everybody played violin, it would sound beautiful. But not as beautiful as if some played cello and some played other instruments."

However a good ear for music and a talent for bringing people together are not all that Dr. Jain takes with him to the laboratory. As a chemical engineer, he believes his mathematical background and quantitative approach to problem solving gives him a unique perspective to basic scientific research.

"One can answer many questions by doing hundreds and thousands of experiments," he said. "But with a mathematical model, one can determine what are the critical experiments. It can help one formulate new hypotheses. The second advantage we have is that we know the basic laws of nature which govern the motion of anything. Chemical engineers are trained in that. Sure, we're trained to apply it to a chemical plant, but ***the laws of physics, the laws of nature which govern motion, and the laws of thermodynamics are the same for physiology."***

Ultimately Dr. Jain hopes his work on tumor barriers will lead to new and better cancer treatments.

"Our first goal is to try and maximize the delivery of oxygen and existing drugs by understanding and modifying the physiology of the tumor — the vasculature and the interstitial compartments.

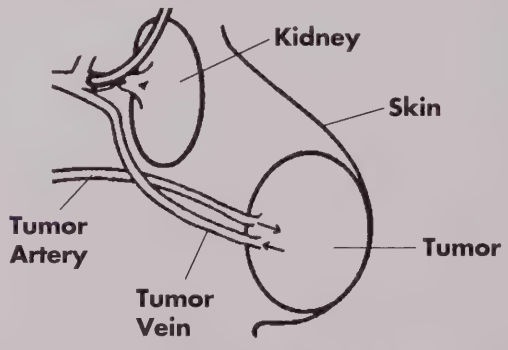
"Our second goal is to develop new therapeutic agents for which the target is not only the cancer cells, but also these other two compartments.

"So it's a different approach and one we hope will pay off in better and more effective cancer treatments." ■

## *How Scientists Study Tumors*

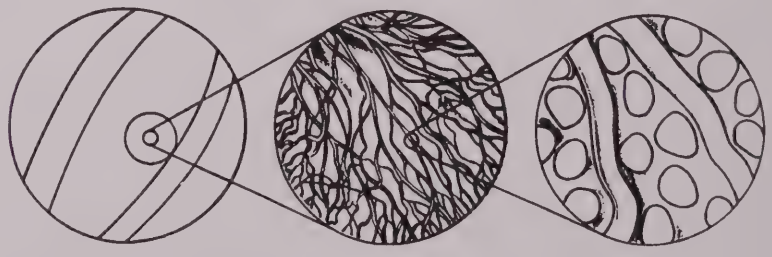
***Single artery, single vein tumor grown in a rat***

*"With this model we can tell how much of a drug enters the tumor and how much leaves, but it's a black box approach because we cannot tell what is happening to the drug inside the tumor."*



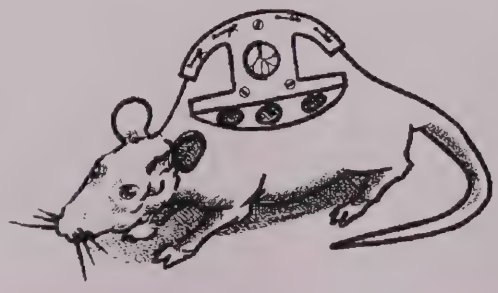

***Thin transparent tumor grown in rabbit ear chamber***

*"With this model we can visualize the entire tumor and what happens to any drug that enters the tumor. The disadvantage is that we cannot grow human tumors in a rabbit."*



***Transparent human tumor grown in an immunodeficient mouse***

*"With this model we are able to follow a human tumor in a live animal in a continuous, noninvasive fashion. We can actually see drugs coming in, where they're going and leaving. It's exciting."*



***The MGH is the only institution in the world with all of these animal models available for studying tumor physiology. "It's a wonderful opportunity," said Rakesh K. Jain, PhD.***

# — MGH Blood Transfusion Service

*(Continued from Page 1)*

for," Dr. Stowell said.

The safety precautions are evident in the statistics. The post-transfusion rate for hepatitis has fallen from 7 to 12 percent a decade ago to an estimated less than 1 percent today. Since 1985, there have been fewer than 20 cases of AIDS from tested blood transfusions reported in the U.S. Dr. Stowell estimates the total number of units transfused during this period at more than 100 million.

"More people will be struck by lightning than will get AIDS from a blood transfusion," Dr. Stowell said.

"Blood is not perfectly safe, but then nothing is. We'll never have a zero-risk blood supply, just like we'll never have zero-risk surgery or zero-risk anesthesia."

The MGH Blood Transfusion Service collects more than 70 percent of the 56,000 units of blood it transfuses each year, making it one of the largest hospital-based blood banks in the country.

"We're as big as some of the smallest free-standing community blood banks," Dr. Stowell said. "Most hospitals do not have their own donor collection services."

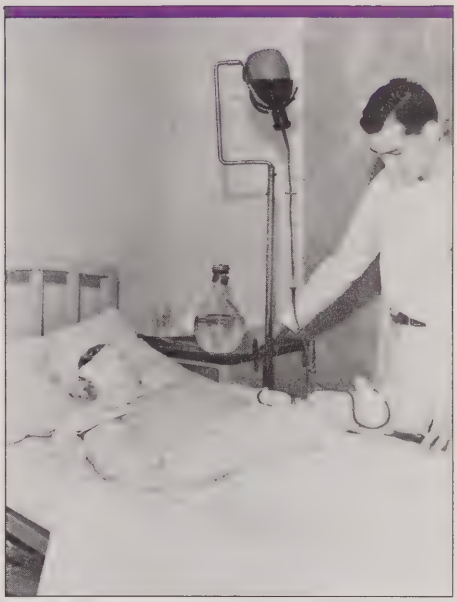
Donor collection has a long history at the MGH. This spring the MGH Blood Transfusion Service — one of the oldest in the country — celebrates its 50th anniversary *(see accompanying story).*

The BTS will mark the anniversary with — what else? — a blood drive.

The need for blood never ceases. In recent years, the aging of the population with its increased demands on health care and services, coupled with more aggressive surgical and medical interventions, has put a continuing demand on donated blood.

One person has anywhere from 8 to 12 units (pints) of blood circulating in his body. Recently a woman undergoing a liver operation at the MGH required 800 units of blood over a three-week period. It is not unusual for a major accident victim to need 200 or 300 units of blood. Likewise more aggressive chemotherapy treatments mean a greater need for more blood transfusions.

To counter this increasing need for blood and to increase the safety of blood transfusions, the MGH and other blood banks have adopted several conservation



methods, including intra- and post-operative blood salvage techniques *(MGH News, October 1974).* During or after an operation a patient's blood is collected, washed, and re-used. "The patient, in essence, ends up being transfused over and over with his own blood," Dr. Stowell said.

Storing one's own blood (autologous donation) — a practice that began at the MGH in the 1960s and has since gained national popularity with the AIDS epidemic — is also encouraged. "Clearly the safest blood is your own blood," Dr. Stowell said. "Many people can be donors for themselves, and so it is a very worthwhile thing to do."

Autologous donation, however, should only be done for planned major surgery. "It's really a waste for patients who are going to have minor procedures that do not use much blood," Dr. Stowell said. "We end up storing the blood on the shelf instead of in the patient's veins."

Other advances to conserve blood use include the development of several naturally occurring hormones such as erythropoietin, which stimulates the bone marrow to produce red cells.

Researchers are also testing the feasibility of using bovine hemoglobin as a substitute for donated red cells.

Only about four percent of all blood transfused today is whole blood. More typically a patient will receive one of the components of whole blood — plasma, which carries the clotting factors in blood; platelets, which are also important for

*(Concluded on Page 6)*

***Above:*** *An MGH resident sets up a blood transfusion for a victim of the 1942 Cocoanut Grove fire.*

***Left:*** *A blood transfusion in 1925*

## — MGH Blood Transfusion Service

*(Concluded from Page 5)*

clotting, or red cells. Red cells contain the hemoglobin molecule, which fastens to (binds) oxygen and carries the oxygen to the tissues.

"Bovine hemoglobin behaves very similarly to human hemoglobin," Dr. Stowell said. `"It can be purified and then transfused as an oxygen-carrying liquid."

About half of all patients requiring a blood transfusion need the oxygen-carrying capacity of red blood cells. Gus Vlahakes, MD, an MGH surgeon who is conducting animal studies with bovine hemoglobin, estimates the number of cardiac surgery patients who could potentially benefit from the substance is around 70 percent.

Bovine hemoglobin also has the potential for a very long shelf life and a virtually unlimited supply, thus eliminating periodic shortages, particularly in Third World countries where there is little blood banking.

"The advantage of having a bovine substitute would be that you would not have to worry about some of the potential immunological complications that we have with human blood," Dr. Vlahakes said. "You also wouldn't have to worry about blood types, so we wouldn't have to go through the cross matching procedures that we have to go through now with human blood."

Currently bovine hemoglobin is being tested in patients at select sites nationwide. Dr. Vlahakes is also testing the potential cardiac surgery applications of the substance in animal experiments in his MGH laboratory.

In sheep undergoing surgery, Dr. Vlahakes replaces about 95 percent of the animal's own blood with bovine hemoglobin. Following the surgery, the animal's blood is returned and replaces the substituted bovine hemoglobin.

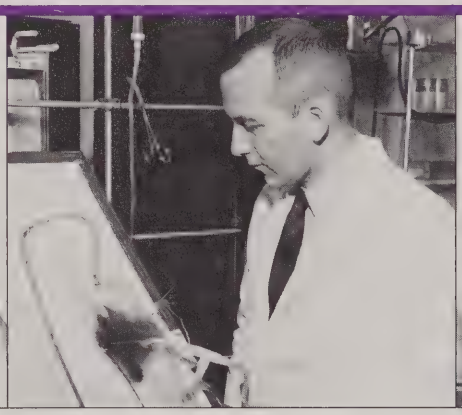
"By using the blood substitute, we can do a major operation with a tremendous blood loss with little ill effect on the animal because its own blood is sitting in the blood bank," Dr. Vlahakes said.

Although bovine hemoglobin still must undergo many more tests before it is ready for widespread patient use, one possible disadvantage of the substance may be its shorter half life in the circulation. "Red cells have a normal life of about 120 days," Dr. Vlahakes said. "It appears the bovine cells may be cleared more rapidly than that, which would mean more frequent transfusions."

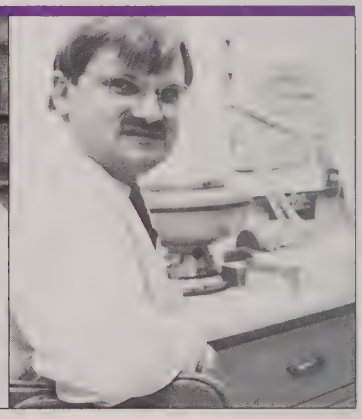
Doctors will not have the definitive word on bovine hemoglobin until all the current patient and animal trials are completed. But cost does seem to be one major advantage of the substance. A cow contains around 20 liters (40 units) of blood. Currently meat packing houses must pay to get rid of the blood. Scientists are only too happy to take it off their hands. ■

*Dr. Lamar Soutter*

*Dr. Morten Grove-Rasmussen*



*Dr. Charles Huggins*



*Dr. Christopher Stowell*

### "Everything Went Wrong in the Beginning"

# MGH Blood Transfusion Service: 50 Years of Giving Life

FIFTY YEARS AGO this spring the MGH opened one of the first blood banks in the country.

Dr. Lamar Soutter — the blood bank's first donor — was also its first director. The service operated out of the basement of a building that no longer exists. In addition to Dr. Soutter, the staff in 1942 consisted of one nurse, one technician, and a part-time maid.

In the beginning, Dr. Soutter later wrote, "everything went wrong." The blood clotted and could not be transfused. Blood that was transfused caused bacterial infections about 12 percent of the time. "Only because of the hopeful tolerance of the hospital administration was the miserable organization allowed to continue its existence," Dr. Soutter wrote of the blood bank.

The administration's patience paid off sooner than expected. In November of 1942, the MGH was flooded with victims of the Cocoanut Grove night-club fire. Four hundred ninety one people died in the fire. The MGH received 114 people, all but 39 of whom died within two hours of arrival. Many of the patients required transfusions with plasma, an important adjunct to the treatment of burn patients discovered at the MGH.

The Cocoanut Grove fire and the hospital's response ended all opposition to the Blood Bank, and it became an entrenched service at the hospital thereafter. Over the years many changes have occurred in blood banking and transfusion practice, some of them pioneered here.

The first blood transfusion at the MGH took place on July 24, 1912. At that time blood was transfused directly from a donor's artery to a patient's vein. One end of a tube was inserted into an artery in the donor's forearm and the other end into a vein in the patient's arm. There was no blood typing or

matching. When no change took place in the patient after 45 minutes, another vein was tried. Still no change. Doctors tried a third vein. After 15 minutes the patient's eyelids fluttered and her cheeks turned pink and felt warm. The donor reported feeling faint.

Later blood was collected in glass bottles — a marked improvement over the direct artery to vein method, which was not only a minor surgical procedure but also destroyed the donor's artery.

But glass bottles had many disadvantages. They were cumbersome and easily broken. Also, blood collected in glass bottles could not be separated into its component parts and had to be transfused whole. Whole blood had a very limited shelf life.

Plastic bags replaced glass bottles at the MGH in 1957. The plastic bags were later improved upon in 1966 with the introduction of triple packed bags which allowed whole blood to be separated into its components for more efficient use and storage.

"The blood was collected in a primary plastic bag, which had tubing connecting it to little satellite bags," said Christopher Stowell, MD, PhD, Director of the MGH Blood Transfusion Service. "We could then take this sealed plastic bag and spin the blood down into its component parts. Since it was soft plastic, the bag wouldn't break. And by doing all the fractionation right in the plastic bag, there was no danger of contamination."

Component therapy greatly increased the number of patients able to be treated with a single unit of donated blood by making it possible and practical to give a patient only those parts of blood actually needed. Red blood cells, for instance, might go to an anemic patient who needed the oxygen-carrying capacity of the red cells. Plasma might go to a burn victim who needed the clotting factors found in plasma. And platelets might go to a cancer patient whose platelet count had been knocked down by chemotherapy.

Spinning whole blood down into its components also increased the storage potential of blood.

Whole blood could only be kept refrigerated for 21 — or at most 35 — days following collection. Researchers knew that if they separated plasma from whole blood, it could be frozen for long periods of time. A major step forward in blood banking occurred in 1963 when Charles E. Huggins, MD, then Assistant Medical Director of the MGH Blood Transfusion Service, perfected his method for freezing red blood cells.

"Freezing blood made it possible to store it for prolonged periods. This gave us a backup supply when the liquid inventory was low. It also made it possible to store rare blood types," Dr. Stowell said.

In the early 1950s most of the blood used at the MGH came either from the families of patients or from paid donors. To improve the reliability and safety of the blood supply, the BTS moved in 1967 to establish an all-volunteer blood program. This program expanded with the purchase in 1976 of a blood donor mobile unit. Today the MGH, which collects about 70 percent of the blood it uses, has one of the largest hospital-based blood donor programs in the country.

In its 50-year history only four directors have led the MGH Blood Transfusion Service. Dr. Soutter, who later became the first Dean of the University of Massachusetts Medical School and is still living, was succeeded in 1952 by Morten Grove-Rasmussen, MD. Dr. Grove-Rasmussen, a native of Denmark, came to the MGH as a surgical fellow shortly after World War II.

Needing some extra money to support his wife and family, he began working part-time in the Blood Bank. He soon came to like the transfusion service so much he gave up all thoughts of a surgical career to devote himself fulltime to the blood bank. Dr. Grove-Rasmussen, who established both the National Rare Blood Registry and the Reference Laboratory System, directed the Blood Transfusion Service for more than 20 years until his death in 1973.

Assistant Director Dr. Huggins succeeded Dr. Grove-Rasmussen in 1973 and ran the service until his death in April 1990. Dr. Huggins was succeeded by Dr. Stowell.

Today, the MGH Blood Transfusion Service occupies the first two floors in the hospital's Gray Building. The service has 120 employees and transfuses more than 56,000 units of blood each year.

"We really do just about everything you can do with blood," Dr. Stowell said. "We collect blood from donors; we make the various components from blood; we do all the testing of blood and screening of donors; we do all the cross matching of blood; we transfuse blood; we do intra-operative and post-operative salvage; we do therapeutic apheresis (a procedure in which blood is withdrawn from a patient, a portion is separated, and the remainder is transfused back into the patient). We have our own computer system and our own donor recruiter. We pretty much cover the whole spectrum. It's a very comprehensive service."

People coming to the MGH today — either as inpatients or outpatients — can only be thankful the hospital administration had the "hopeful tolerance" 50 years ago to continue the vital, life-giving service. ■

# DXplain: RX for Physicians Facing a Difficult Diagnosis

THE YOUNG FAMILY physician in West Texas had never before seen a patient with a combination of symptoms quite like this.

His patient, a child, had severe abdominal pain but no stiff neck (meningitis). He alternately ran a dangerously high fever or chattered with chills. Most puzzling of all, the boy had a rash on his wrists, his ankles, and the soles of his feet.

The doctor typed the boy's symptoms onto his computer terminal and asked for its help. Much to his surprise the computer typed back a suggested diagnosis of "Rocky Mountain Spotted Fever," an acute infectious disease spread by a tick indigenous to the mountainous regions of Montana and Idaho, the eastern seaboard, and the southeast. West Texas is not part of the tick's natural habitat.

Despite the computer's curious suggested diagnosis, the doctor ran one of the tests mentioned by the computer. Sure enough the test confirmed Rocky Mountain Spotted Fever.

The doctor had only one thing left to do. He checked back with the patient. Two weeks before the child had been hiking with his family in Colorado.

It is not surprising that a family physician in West Texas would know little about Rocky Mountain Spotted Fever. That is why he consulted DXplain, a comprehensive computer-based medical information system.

DXplain contains information on more than 2,000 diseases: "That's many more diseases than any of us anywhere has any real knowledge about," said G. Octo Barnett, MD, Director of the MGH Laboratory of Computer Science, who developed the computer program. "You cannot make a diagnosis if you don't think about the disease in the first place."

DXplain, which provides up-to-date medical information to doctors faced with a difficult diagnosis, is now available either as a stand-alone software program or through a new nationwide computer

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## — DXplain

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network called U.S. HealthLink. DXplain is the only diagnostic medical support system available over a computer network.

"What it means is that any physician, whether he or she is practicing out in the boondocks or in a medical institution, has access to this comprehensive medical knowledge," Dr. Barnett said.

The U.S. HealthLink hookup marks the second time DXplain has been made available over a nationwide computer network. The American Medical Association carried DXplain over a national computer network during the mid-80s (MG*H News, March 1989*). As many as 20,000 physicians subscribed to the AMA network before it was abandoned by AMA for financial reasons about two years ago.

The DXplain program available today is considerably different from that first version. Over the years Dr. Barnett and members of the Laboratory of Computer Science have continued to modify and simplify the user interface program to improve access to it.

To keep up with the constantly changing flow of medical knowledge, the content continues to be updated on a regular basis. A built-in feedback system allows users to type in comments and suggestions. User comments provide a valuable quality control check and a source of material to be included in the quarterly updates

"We see it as a continually evolving program," Dr. Barnett said.

Dr. Barnett, a former cardiologist who founded the MGH Laboratory of Computer Science, first began work on DXplain 10 years ago. "I've always been interested in the potential application of computer technology to diagnostic reasoning," he said. "Diagnosis is basically a probablistic type of decision making."

DXplain does not make a diagnosis but it does use the probabilities of the occurrence of the signs and symptoms to suggest diseases which should be considered.

Most medical textbooks are written from the disease backwards. "If a patient has congestive heart failure, you read the chapter about congestive heart failure. If he has anemia, you read the chapter about anemia," Dr. Barnett said. "The trouble with that approach is that patients don't present with labels, they present with symptoms."

DXplain is written from the other direction. A doctor can type in a set of signs and symptoms and obtain a list of diseases to consider. A doctor can also use DXplain like a medical textbook to obtain general information and literary references on the more than 2,000 diseases contained in the program.

DXplain is a valuable tool, but Dr. Barnett stresses that it is only that — a tool. "It's important for physicians to remember that they always know much more about the patient than what they've told the computer. Computers can also be wrong just like people can be wrong."

But in this era of instant communication and constantly changing medical knowledge, DXplain can be a valuable support system. Physicians, group practices, and hospitals can benefit from DXplain either as a stand-alone computer software program or as a hospital information system through the U.S. HealthLink network.

"Medical decision making requires us to be able to access a very diverse and complicated set of medical knowledge," Dr. Barnett said. "DXplain is another way to access that knowledge." ■

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MGH News

Massachusetts General Hospital, Boston, Massachusetts Vol. 51 No. 4 June-August 1992

# Flexible Monitoring Changes Care at MGH

RITA JOHNSON admits she waited too long before seeing a doctor about her chest pain. "I'm the kind of person who keeps thinking it will go away. But this time it didn't go away," she said, sitting up cheerfully in bed in the MGH Cardiac Access Unit.

"Now I'm in for a cardiac catheterization and a triple bypass," she said as an EKG and pressure measurement apparatus sent continuous signals to a small, white box on a bedside stand. An intravenous dose of nitroglycerin trickled into her right arm.

Had it not been for that white box, Rita Johnson might not have been resting so comfortably in a "general care" patient room in the Cardiac Access Unit, a portion of the Ellison 6 patient care area.

"She is definitely someone who would have been in the intensive care unit (ICU) before we had the ability to move monitoring equipment to patients on an as-needed basis," said Nathaniel Sims, MD, an MGH cardiac anesthesiologist who, with James P. Welch, CCE, and Penny Ford-Carleton, RN, is one of the system's co-inventors. "She's getting a very high level of medication. We could not use these drugs without having some kind of continuous vital signs surveillance," Dr. Sims explained.

The monitor and its centralized computer work station at the nurses station down the hall are part of the "flexible monitoring" system, a potential groundbreaking change in patient care at MGH.
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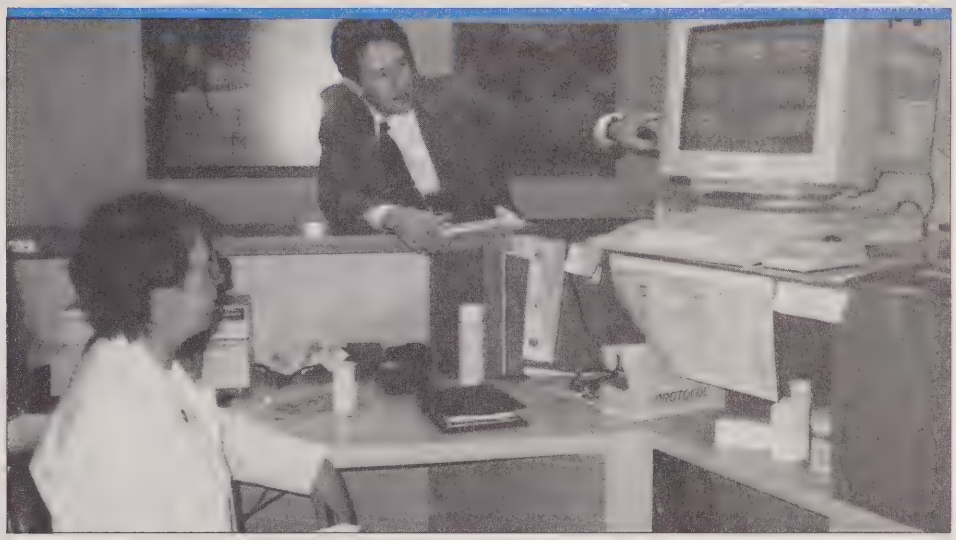


*Dr. Nathaniel Sims, who is a co-director with Penny Ford-Carlton, RN of the flexible monitoring system, works with research nurse Roberta Nemeskal, RN, on the system's central work station on the thoracic surgery floor.*

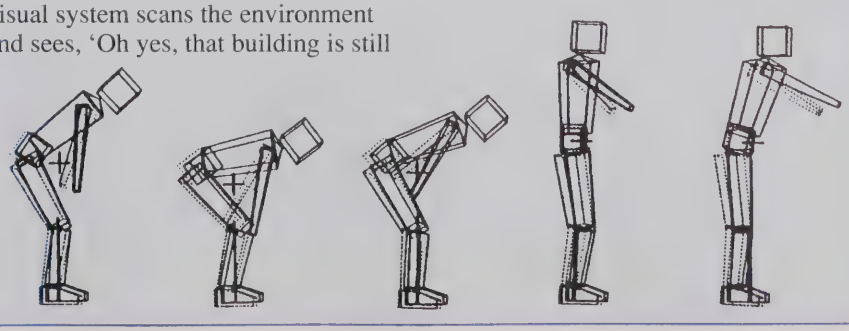
## Biomotion Lab Moves to New Problems

IMAGINE sitting on a train and looking out the window when the train next to you begins to move.

"You have a moment of disquietude. You think, 'Hey, I'm moving,' But then you realize something's wrong," said David E. Krebs, PhD. "You're not really moving."

Most people quickly realize that it is the train beside them moving. "Your visual system scans the environment and sees, 'Oh yes, that building is still stationary relative to me. It's the other train that's moving,'" explained Dr. Krebs, Acting Director of the MGH Biomotion Laboratory.

But for a small group of people who have disorders of the inner ear, such experiences can be traumatic. "They might get dizzy, fall over, or in some cases vomit," said Dr. Krebs. "Those
*(Continued on Page 2)*



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EDITORIAL

# Is Public Service Dead?

IT IS NO SECRET THAT AMERICA is going through a time when the ordeal of public office is threatening to turn politicians into an endangered species. In part that is because television holds candidates to the scrutiny of the potential voter who sees the aspirant close up, "warts and all." Add to this, journalists who think everything about a politician's past is fair game, whether fact, fiction, gross exaggeration, or rumor — regardless if relevant or immaterial — or if recent or 40 years ago. Some of the penchant which often leans toward the prurient has long inhabited this planet. Lot's wife turned into a pillar of salt because of her need to see what was happening to Biblical Sodom and Gomorrah. Hollywood has traditionally suffered from the sin-and-tell syndrome which supermarket pulps thrive on. The sports hero of yesterday — even Babe Ruth — wears the clay feet of today.

So it is no surprise that physicians, once deified, are now as a group often reviled. Some of the public, expecting medical miracles, clamor for the physician's wallet whenever the reality of what is possible takes shape in a given patient's less-than-perfect results. With the patient demanding the scalp of the sometimes guilty, sometimes innocent doctor, being wedged between physician and public is a hazardous position.

Nobody has a more precarious perch than the chairman of the Massachusetts Board of Registration in Medicine. Ask Dr. Dinesh Patel, the MGH arthroscopic specialist, who currently chairs that board. A page 7 article in this issue features Dr. Patel and the board's impossible task. Whatever action the board takes is bound to attract complaints. To some of the public anything short of revocation of an accused physician's license to practice is a dereliction of duty. To some of the medical profession too many findings against physicians make the Board appear villainous.

Given the above, one wonders why anyone ever agrees to serve on the unpaid committee, let alone as its unpaid chairman. To them one can point and say, "Maybe public service is not dead." ■

## — Biomotion

*(Continued from Page 1)*

whose inner ear, the vestibular system, is not working properly have trouble functioning in moving environments because they cannot orient themselves in space when things around them are moving."

A vestibular disorder, a particular type of balance disorder, is one of the motion problems that can be analyzed at the MGH Biomotion Laboratory, which is now expanding its patient care services. Eight years of research at the lab have provided the staff with a wealth of knowledge about the way people walk, sit, stand, run, and balance themselves. ***Now, with the support of the MGH Orthopaedics Department and Physical Therapy Services, the lab is offering its services to patients and physicians dealing with problems ranging from artificial limbs to cerebral palsy.***

***Originally established with a grant from the Edwin Phillips Trust to study the motion disorders of children with cerebral palsy, the Biomotion Lab continues to work with the cerebral palsy population but now also examines a wide array of patients with other disorders including problems caused by arthritis, strokes, athletics, neurological impairments and musculo-skeletal difficulties.***

People with knee or hip replacements are commonly seen at the lab, where clinicians can use their state-of-the-art, three-dimensional computer program to analyze problems with such tasks as climbing stairs and getting in and out of a chair.

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Treatment approaches can therefore be advanced or further developed based on this information. Such approaches may involve exercises or adjustment to the artificial joint.

"You're never going to be as good as you were made in the first place," Dr. Krebs explained. But using the type of analysis available at the Biomotion Lab, a patient can make the best possible use of a new limb or joint.

The computerized three-dimensional motion analysis system is the heart of the Biomotion Lab. The four-camera system, combined with an advanced computer software program, has enabled the Biomotion staff to create a visual, three-dimensional moving computer model of the human body in action. The movements, stresses, and forces of the patient in motion can be measured with extreme accuracy and analyzed for problems.

"This lab is essentially home-grown and unique," said Technical Assistant Director Patrick Riley, PhD. Based originally on a two-camera system developed at MIT to look at one side of the body, the MGH Biomotion Laboratory further developed it into a four-camera system that can look at the entire body.

When patients with a balance disorder come to the lab, for example, the 3-D computer analysis system is used to help diagnose their condition. Then the patient can proceed with further clinical evaluation and treatment through Physical Therapy Services. "We do a detailed evaluation of which eye, head and body movements cause symptoms," said Kathleen Gill-Body, MS, PT, NCS, board-certified clinical specialist in neurological physical therapy.

There are three human systems that help a person maintain balance while in motion, Ms. Gill-Body explained. They are the visual system, the inner ear, and the musculo-skeletal system of the legs and feet, also known as the somato-sensory system. If one of the three systems is not working (the inner ear, for example), it is possible through treatment to develop the other two systems more fully to compensate, like a blind person who relies on his senses of touch and hearing. The computer system is used to help determine if the

treatment is effective in improving balance. The 3-D system records and analyzes the person's movements while he or she walks over an irregular surface, Ms. Gill-Body said.

A patient who is found to have little or no inner ear function is then given exercises to help develop the visual system and somato-sensory system. "This person is going to be very unstable," Ms. Gill-Body said, "When he or she moves, the world is going to jump. He or she is not going to be able to manage a fixed gaze when moving."

To develop his visual system, the patient practices focusing on a stable object while he is walking around to improve his sense of visual stability. To develop the somato-sensory system, the patient practices standing still while keeping his eyes closed.

Another type of patient commonly seen at the Biomotion Laboratory is someone with artificial limbs or joints. In one instance, a man in his 60s was referred by a surgeon who planned to do a knee replacement operation.

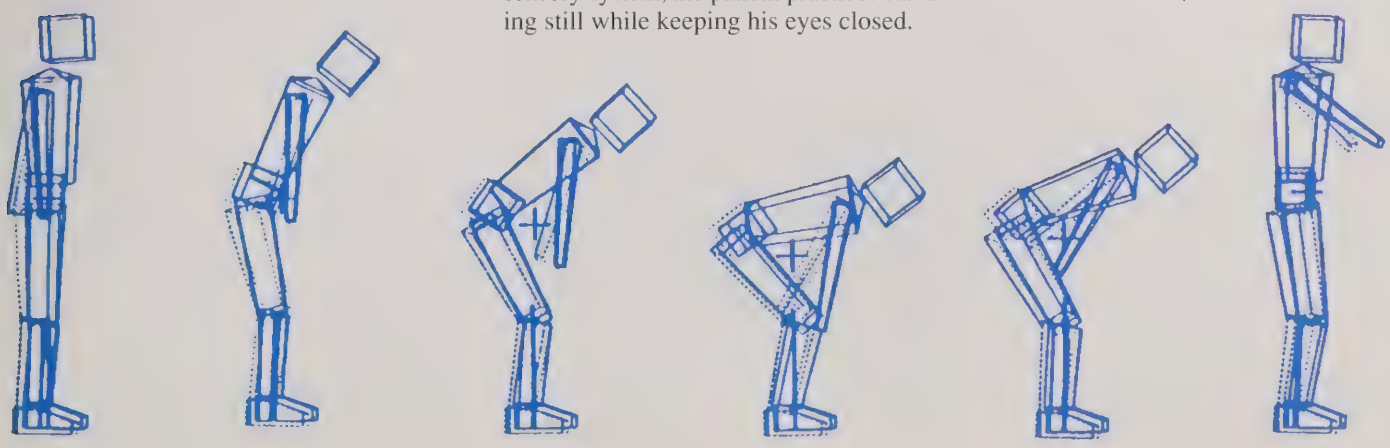
"The man was a woodsman," Dr. Krebs said. "He had a forest and complained that he couldn't do his logging work. We analyzed the movements of his knee before the surgery and discovered there were excessive forces on arthritic areas of the joint. After the knee replacement operation the lab did a similar analysis at 6 weeks, 6 months and again at one year.

"We were able to determine that he needed to do more strengthening with his eccentric muscle exercises. That's the type of motion you use when you're descending the stairs. His knee was buckling." Ultimately, the man was able to go back to his logging work in the forest.

The beauty of the computer system, said Dr. Riley, is that it allows clinicians to base their treatment and therapy on fact, not opinion. The ability to make precise measurements means that it is possible to sort out whether a person is getting better as the result of therapy or whether the improvements are due to other factors.

"I think that one of the hardest things to sort out in the rehabilitation field is that when you're dealing with a person, just the fact that you're dealing with him and he is doing something is a big benefit in itself," Dr. Riley said. "It becomes difficult to say what part of the performance improvement is due to the therapy and what part is due to the fact he is just doing something."

The motion analysis system takes the guesswork out of the diagnosis. Much of the trial and error process can be eliminated because of the computer's capability to ascertain the stresses and forces of the smallest movements of virtually any part of the body. "The result is greater precision in the treatment," Dr. Krebs said, "If it can be measured, we can measure it." ■



## — Flexible Monitoring

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For the first time, patients need not be moved back and forth between the intensive care unit and other areas of the hospital as the need to monitor their vital signs changes. Now, patients who need continuous monitoring but don't need the intensive nursing care of the ICU can remain on the general care floors with the use of the new portable, bedside monitors that keep track of heart rate, oxygen levels, and blood pressure. In addition, patients in the Emergency Department who need to be admitted to the hospital may not need to face extended waits for "monitored beds."

The flexible monitoring system, developed through the MGH Department of Anesthesia's Bioengineering Unit in collaboration with Protocol Systems Inc., of Beaverton, Oregon, may significantly help to relieve a major stress on hospital resources: the logistical rigmarole associated with moving patients from one location to another. Called the "flexible monitoring" system, it provides continuous monitoring of vital signs right at the bedside, and at the nurses station. Cardiac patients can remain in the cardiac unit, urology patients in urology, surgical patients can remain on the surgical floors, etc., where specially trained personnel are attuned to the specific needs of patients.

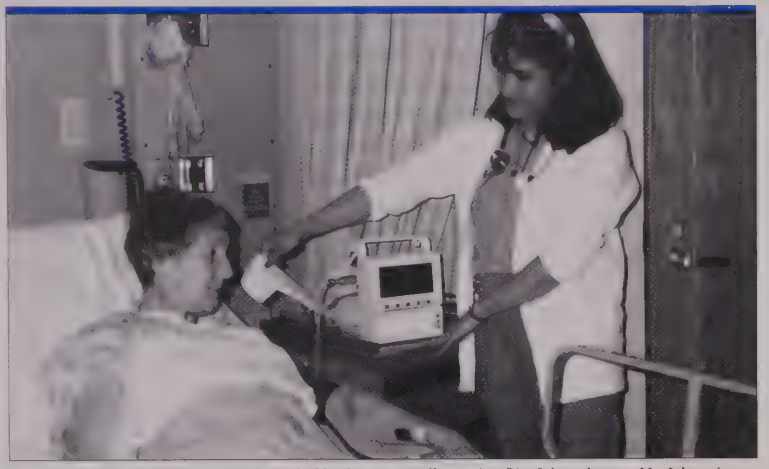
"It's hard to assess the exact savings," said Penny Ford-Carleton, RN, co-director of the flexible monitoring project. "But moving a single patient from one place to the next involves a significant amount of time and 'hassle,' and numerous communications with the medical and nursing staffs, admitting office, dietetics services, and environmental services.

"There is a tremendous ripple effect throughout the hospital each time a patient is moved."

Already, health care facilities elsewhere are embracing the technology. The Mayo Clinic, The University of Alabama Hospital, an outpatient dental surgery clinic in Washington, and hospitals in Denmark and Canada are installing the MGH-Protocol developed monitors and work stations, Dr. Sims said. "By the end of 1992 perhaps 20 to 60 systems will be in place in several countries."

Installed initially on two 'clinical trial' floors at MGH in 1991, Ellison 7 and Ellison 13, flexible monitoring now involves the use of 120 bedside monitors on 12 floors including general surgery, thoracic surgery, urology, cardiac access, and general medicine units. The monitors can be unplugged and easily carried wherever needed. This flexibility contrasts dramatically with the fixed nature and high cost of traditional bolted-in-place monitoring systems used in intensive care units and costing $15,000 to $25,000 per bed. A flexible monitoring installation typically costs between $2,500 and $4,000 per networked location.

A study of the impact and the effectiveness of the system for the first 1,000 patients to use it is currently underway, says research nurse Roberta Nemeskal. "We are trying to make sure, among other things, that we don't have patients who require intensive care on the general care floors."



*Cardiac Access nurse Dianah Lapus adjusts the blood pressure cuff on patient Rita Johnson's arm. Ms. Johnson's blood pressure reading is continuously monitored by the portable device on the bedside stand that is part of the new flexible monitoring system.*

With hospitals admitting increasingly sicker patients, there is a blurring of differences in monitoring requirements between the ICU and general floors. "There is an increasing demand for monitoring outside the ICU," said Ronald S. Newbower, PhD, the MGH's Vice President for Research and Technology Affairs. "It is now possible to bring the technology to the bedside," he said. The small portable monitors mean that "you don't have to equip every bed," said Dr. Newbower. Instead, a portable monitor is placed on a bedside stand and plugged in wherever needed.

Each small monitor is connected to a main computer work station where nurses can observe the condition of up to 16 patients at one time. An alarm sounds at the central station and is displayed on hallway message panels if a patient's vital signs fall outside of preset limits. Nurses can look at the screen or the hallway signs to see instantly which patient is affected and take appropriate steps to resolve the problem.

Patient Rita Johnson, 77, waiting for her bypass surgery, could see the value of the new system. "The nurses don't have to keep running in here all the time to take my blood pressure," she explained, "yet I feel I am being 'closely watched.'"

Designing the system so that it would increase the nurses' efficiency was part of the challenge, said Ms. Ford-Carleton. "We wanted to make sure it would be something nurses unfamiliar with a computer could use easily and intuitively," she said. With this in mind, extensive human factors testing was conducted with the nursing staff on Ellison 7 and Ellison 13. The computer software was designed with recognizable pictures or icons telling nurses the status of each patient's condition. A green smiling face indicates all signals are stable, for example. A red heart shape indicates an alarm in one of the measurements. In addition, a 'trackball' and cursor for point-at 'buttons' on the screen simplify system operation.

The system is also adaptable to different circumstances. On one floor the percentage of oxygen in a patient's blood is considered a primary indicator of a patient's condition while on another floor, blood pressure is more important. The system can be programed to monitor any combination of several vital signs including EKG (electrocardiogram), blood pressure, temperature, heart rate, and oxygen percentage.

Refinements are continually underway, Dr. Sims said. For example, patient movement was found to cause distortion in some readings, sometimes leading to an unacceptable number of "false alarms." Further refinements have eliminated some of the distortion caused when a patient moves, reducing the number of alarms. Dennis Gurgul, Clinical Engineer, who maintains the computer networking portion of the system, pointed out the power of the computers to collect performance and alarm data which can be used to direct and evaluate refinements to the system. "With the computer we are using, we will also have the ability to interface with other hospital systems and exchange information," he said. In addition, telemetry or 'wireless' monitoring capability is being added on some MGH installations, allowing ambulatory patients to move about freely without cables tethering them to the monitor, within a range of about 150 feet of the bedside monitor, while their vital signs continue to be monitored.

"All they need is a small box that hangs around their necks to send EKG signals to the bedside monitor in their room," Dr. Sims said. "This is particularly useful on the general care floors where patients are often encouraged to move about as part of the recovery process."

Although Dr. Newbower first conceived the idea for flexible bedside monitoring on the general care floors ten years ago, medical electronic technology was not advanced enough to seriously consider designing such a system until the past few years. In 1989, he convened a special MGH task force to evaluate ideas for bedside technology. Options were carefully considered, and Protocol Systems, Inc. was selected from among several companies which had expressed interest in designing the system in collaboration with MGH.

"The time cycle for this joint development effort is strikingly short," Dr. Sims said. "From March of '89 for the idea, to March of '90 for the beginning of the development process, to April '91 for the first clinical system, to November, '91 for FDA approval. We're pleased that we were able to keep a brisk pace of development from start to finish."

The bottom line, of course, is patient care. Allowing patients to stay wherever medically appropriate in one familiar setting on a general care floor without shuttling them back and forth to other care settings can reduce stress on both staff and on the patient.

"I didn't have any of this business of being moved from room to room, chased from place to place," said one 74-year-old patient with long-standing mild heart disease and colon cancer. "I didn't have to get to know a place that's not familiar to me," he said. "And that's a stress."

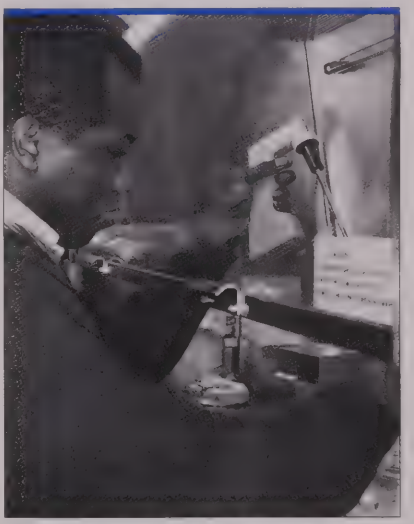
The MGH owns rights represented by the patent application and has licensed them to Protocol Systems. The hospital receives a small royalty from sales of the system marketed under the trade name 'Acuity.' In accordance with standard practices with royalties, specified portions are distributed to inventors, to the Department of Anesthesia, and to the hospital. ■

# *Foundations: Critical to Research Support*

THERE ARE MANY WAYS in which cancer may begin — a gene goes bad, a receptor goes haywire — but no matter what the cause, the bottom line, said Gerald L. Waneck, PhD, is that our bodies should be able to deal with the defect.

"It's the responsibility of the immune system to get rid of any defective cells," said Dr. Waneck, an Associate Biochemist in the MGH Surgical Service.

Dr. Waneck had some ideas about why the immune system fails to attack cancerous cells, but it wasn't until he received a small pilot grant through the American Cancer Society's (ACS) junior investigator program that he could begin to test them. He decided to look at the "trafficking" patterns inside epithelial cells (covering of internal and external body surfaces) because 85 percent of all cancers arise there, Dr. Waneck said.



*Research Technologist Carl Rollins is involved in ongoing research into the immune system's ability to fight cancer, a study funded by the American Cancer Society and the National Institutes of Health.*

In order for a cell to work properly, it must transport certain molecules to one surface of the cell or to the other. "The cell has a very high organization," Dr. Waneck said. But cancer disrupts the cell's normal organization and trafficking patterns, and that's where the ACS grant comes in. Dr. Waneck is looking at how the system is supposed to work.

"It's a wonderful program that the ACS has," Dr. Waneck said. "They are looking for junior investigators who don't already have strong support but who have some promising ideas."

Dr. Waneck's investigation of epithelial cells is a good example of how foundation grants fit into the complex funding picture at the MGH. In sheer dollars, grants from foundations make up only a small percentage of the total research funding. Roughly 50 percent of the total comes from the federal government. Grants from industry make up another 25 percent, and

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# — Foundations: Critical to Research Support

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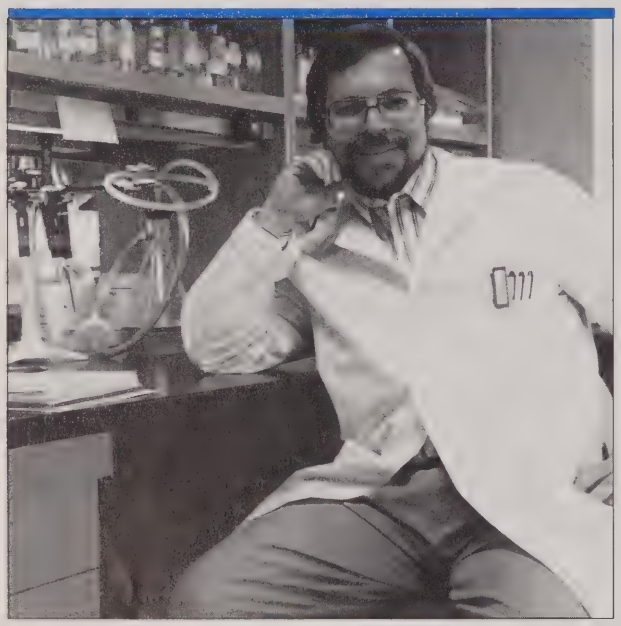
foundation grants comprise about seven percent. Funding from foundations has been rising slowly in recent years, from $5.1 million in 1987 to a projected $6.3 million this year. There are more than 50 foundations that grant anywhere from $2,500 to $1 million or more to the MGH annually.

But statistics don't tell the whole story. In the case of foundation funding, "its magnitude and importance is far greater than the magnitude of dollars," said Ronald S. Newbower, PhD, Vice President for Research and Technology. "That's because foundations are often more willing to fund the kinds of research that government or industry won't touch. They will take the risk that conventional funding agencies can't or won't. This is particularly important to young investigators." A small grant from the ACS can provide "that crucial, early support and the validation to a young investigator that shows they're on the right track. It shows they have achieved credibility, and it can launch a productive career."



*Dr. Gerald L. Waneck, a biochemist in the MGH Surgical Services, received an $8,000 American Cancer Society award that funded the cancer research leading to a National of Institutes of Health grant*

With the $8,000 ACS grant, for example, Dr. Waneck provided the data on epithelial cells that convinced the National Institutes of Health (NIH) to fund on a wider scale a million dollar MGH study of the same subject.

"It's an award that means something beyond the money," Dr. Waneck said. "It's the recognition from the institution and from one's colleagues. It gave me confidence that I was working on something worthwhile. And it helped me start a new project that led to the NIH funding."

ACS Chairman of the Board Stanley Shmishkiss said that obtaining an ACS research grant is becoming more competitive because the number of applications is rising rapidly. "We are only able to fund 12 percent of the total approved applications," Mr. Shmishkiss said, despite the fact that the total amount of funding ACS supplies nationally ($94 million this year) has been rising gradually.

The American Heart Association (AHA), too, has been receiving more applications for grants, said spokesman Howard Lewis. During the 1990-1991 fiscal year, the AHA was only able to fulfill 22 percent of the requests for grants with $95.1 million compared to the 30 percent that were funded in 1988-1989, Lewis said. Larger organizations like the ACS and AHA also provide major, as well as smaller grants. The ACS, for example, has awarded Edward E. Harlow, Jr., PhD, Director of the MGH Laboratory of Molecular Oncology at the MGH Cancer Center, with a $50,000-a-year lifetime grant for his work (*MGH News*, May 1991); and recently, a $300,000 grant to Dr. Patricia K. Donahoe, Chief of Pediatric Surgery, for her research on ovarian cancer.

Foundation grants play another critical role in funding at the MGH because they often help fill in the gaps between other, larger sources of funding, said MGH General Director Dr. J. Robert Buchanan. There are three types of foundations, each playing a different role, he said. The large public foundations such as the American Cancer Society and the American Heart Association fund research in their own broad areas of interest.

Next there are the large private foundations like the Pew Charitable Trust, which funded the MGH Radiology Unit and the Medical Service to the tune of $285,876 last year and the Robert Wood Johnson Foundation, which gave a total of $193,688 to the Anesthesia Department and Medical Service. These groups set out specific goals and objectives for their funding, Dr. Buchanan said. "We go to them when we have a project that fits their guidelines."

For example, the Markey Charitable Trust recently announced a $3 million cancer research grant to be awarded over five years that fills an important funding gap. With this grant, the MGH hopes to hire two new assistant professors to do research in molecular oncology. The grant is important because it fills a funding gap for physician-scientists who hold both the MD and PhD degrees. For MDs without a PhD, NIH funding is available, but a researcher with the MD-PhD combination cannot currently be supported by the NIH Physician Scientist or the Clinical Investigator Award.

While the larger foundations may have highly specific funding goals, Dr. Buchanan said, the smallest, private foundations are often quite flexible, and their moneys fill gaps that otherwise might be difficult to fund. "It's sort of like the chinks between the logs of a cabin," Dr.Buchanan said. "The big foundations lay the logs and the small foundations fill in the gaps."

Examples of small foundation grants include $19,370 from Aid for Cancer Research to the Pediatric Surgical Service and the Urology Service. The American Federation for Aging Research granted $22,500 to the Neurology Service and $5,000 to the Pathology Unit.

Overall, private foundation funding will play an important role in the $160 million Leadership Campaign, announced recently, said Chairman of the Board of Trustees Ferdinand Colloredo-Mansfeld.

The hospital is seeking to reach this fund-raising goal by December of 1997, explained Allen Peckham, Vice President of Resources and Development. Of the Campaign total, he said, $35 million has already been raised. Two thirds of the Campaign will support patient care and research programs. The remaining funds will help complete the Tower II project.

"Considering the increased competition for the philanthropic dollar here in New England and across the nation," Mr. Colloredo-Mansfeld pointed out, "the hospital's success in securing gifts from private foundations will be even more critical to reaching our goal." ■

*Board of Registration in Medicine*

# Discord Sometimes Indicates Harmony

Dinesh Patel, MD, has not eaten lunch in the MGH cafeteria in four years.

"Usually I just grab a coffee and doughnut and go off in the corner somewhere," said the Chief of the Arthroscopic Surgical Section of the Department of Orthopaedic Surgery.

Coffee and doughnuts and lunch in the corner. Such is the price of public service.

It is not that Dr. Patel dislikes people. On the contrary, he is one of the most popular physicians at the MGH. It is just that as Chairman of the Massachusetts Board of Registration in Medicine, Dr. Patel occupies one of the most sensitive posts in medicine. He is quite literally in the hot seat, answerable to two masters — the public and fellow physicians. MGH professionals often volunteer for unpaid public service, and Dr. Patel's role demonstrates the pressures such civic duty can exert. No wonder he eats lunch by himself. "It's important for me to maintain my independence," he says.

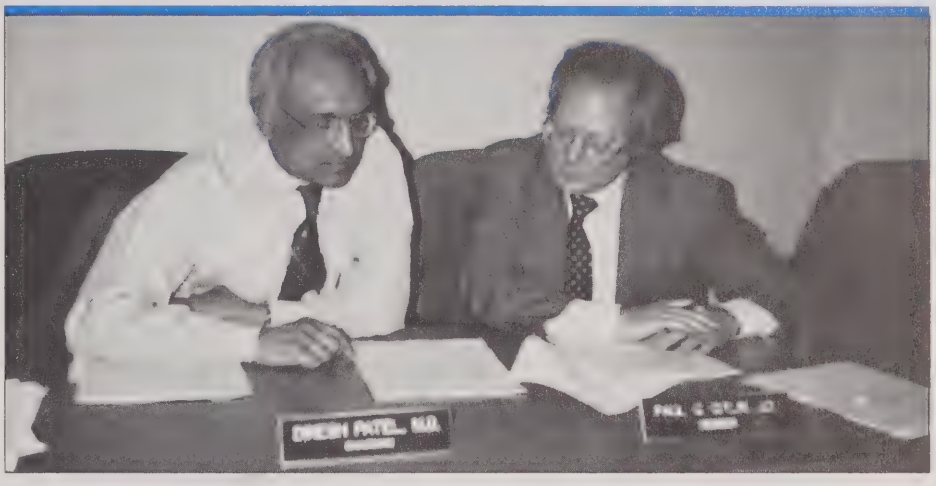
The Board of Registration in Medicine is 1 of 10 state agencies within the Office of Consumer Affairs and Business Regulation. The board is charged with promoting and maintaining a high quality of health care in the state by *protecting the safety, welfare, and rights of the public and the rights of physicians.* As such it has four main functions.

- Licensing: The board oversees and processes the license applications and renewals of the 23,000 physicians registered in Massachusetts.
- Data Repository: The board serves as a repository of information from insurers, hospitals, and professional associations on violations by licensed physicians.
- Patient Care Assessment: The board oversees the development and implementation of risk management programs at hospitals and health care facilities throughout the state.
- Discipline: The board oversees, investigates, and acts on the roughly 700 complaints it receives each year from consumers.

The seven members of the board include five physicians and two members of the public. They are all appointed by the governor and serve for three-year terms. Dr. Patel, who was appointed by former Governor Michael S. Dukakis, is in his second three-year term, and second one-year term as chairman. In both elections his fellow board members unanimously elevated him.

"I was interested in serving society in some manner and helping to change policies that could be hurting the public or hurting physicians," Dr. Patel said. "In my own practice I strive to provide first rate quality of care.

"If you preach first rate quality of care, you should try to provide first rate quality of care in policy making as well if you have the opportunity. That's the reason I got involved with the board."




*Dr. Dinesh Patel, Chairman, and Paul G. Gitlin, Vice Chairman.*

Dr. Patel took over the chairmanship in January 1991 at a particularly difficult period. There was a new governor and a new party in power, four new board members, and a public angry and upset at what it considered the board's go-soft attitude on physicians. At the same time the state's doctors were upset at what they felt was overly harsh treatment by the board. The atmosphere was so charged, in fact, that Secretary of Consumer Affairs Gloria Cordes Larson in July 1991 appointed a "Blue Ribbon Task Force" to review the policies and operating procedures of the board.

"It was an extremely difficult period," said Philip E. McCarthy, MD, President of the Massachusetts Medical Society. "There was a real 'us versus them' atmosphere that surrounded the board."

"The board has always been somewhat controversial," added Stephen G. Wallace, Assistant Secretary of Consumer Affairs and Chairman of the Task Force appointed to investigate the board. "The pendulum of public opinion on the board has always swung back and forth between being too pro-consumer or too pro-doctor."

When Dr. Patel took over the board, the pendulum was swinging almost out of control.

"The criticism we got a couple of years ago from consumer groups about not disciplining enough doctors and from doctors about being too hard was unbelievable," he said. "I finally told people, 'Look, we don't keep a quota. Our criteria is quality of care.' We act on a case-by-case basis. This means we don't want to discipline every doctor unless discipline is warranted. But at the same time we don't want to leave any stone unturned no matter where it leads. It's been a very difficult task."

At least some of the acrimony surrounding the board a few years ago seemed to lie in the numbers coming out of the board's Disciplinary Committee and the perceptions and misperceptions created by those numbers.

In 1987 and 1988 the number of doctors disciplined by the board peaked at 96 and 95, respectively, leading to numerous complaints from physicians.

By 1991 the number of disciplined doctors had declined to 31, fueling complaints from consumer groups that the board had suddenly gone soft on physicians.

Neither side was right. A look behind the statistics explains.

One reason for the large number of disciplined doctors in 1988 and '89 can be traced back to 1986 and an increase in the board's budget that year. The increased funding allowed the board to hire more staff and process more cases — many of them pending for many years.

"Simply because we had such a large backlog of cases and more staff to process them, more doctors were disciplined," Dr. Patel said.

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## — Board of Registration

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Today the board is seriously underfunded and understaffed. Backlogged cases again began to mount. Over the last year, however, new reforms have helped reduce the backlog dramatically despite the lack of resources.

Changes in board practices contributed to the decline in the number of disciplined doctors. Prior to 1988, out-of-state physicians who held a Massachusetts license but who practiced and were disciplined in another state, were also automatically disciplined in Massachusetts. Now the board does not revoke a doctor's license until the physician actually moves to the Bay State.

The board's progressive handling of chemically dependent physicians has also led to a decline in the number of disciplined doctors. Under Dr. Patel's leadership the board has adopted a national standard of treatment and rehabilitation — rather than punishment — for doctors with a chemical or psychological dependency.

Instead of revoking a physician's license, the board suspends it, allowing the physician to continue practicing under supervision while receiving treatment and counseling. The treatment is administered in cooperation with the Physicians Health Program of the Massachusetts Medical Society.

"It's a compassionate approach to discipline," Dr. Patel explained. "We recognize the physician's problem is a disease that needs treatment not punishment. As long as the doctor's not hurting patients, we want to treat the disease."

Dr. Patel has also worked to ease tensions between physicians and consumer groups by expanding the board's outreach efforts. His philosophy is that more education can lead to fewer misunderstandings.

"Many people don't really know what we're all about," Dr. Patel said. "We want to strip away some of the misperceptions and misinformation."

At the same time he does not want the educational process to be one-sided or one-directional. He encourages public interest groups and private citizens to "contribute to the intellectual discussion" in an effort to make the board more responsive. "Unless people tell us their concerns, we don't know what they are," he said.

Dr. Patel, who is also an Assistant Professor of Orthopaedic Surgery at Harvard Medical School, attributes the smooth functioning of the board to his fellow board members whom he calls "seven intellectual giants." He also stresses the support of Executive Director Alexander "Sandy" Fleming, General Counsel Penny Wells, and Secretary Larson, for their input and contributions.

But policy changes, teamwork, and outreach efforts are not the only reasons for smoother relationships between the board and its opposing constituencies.

Dr. Patel's easy-going personality and consensus-style leadership have also helped cool tensions and tone down the rhetoric.

"He's a great listener," Dr. McCarthy said. "He likes consensus. It has allowed people on all sides of an issue to trust him. It's quite a balancing act."

Dr. Patel's open style and willingness to listen to all sides was probably best exemplified during the recent task force investigation of the board.

"He was very supportive of the investigation," Mr. Wallace said. "He made the board staff available to us. There was no sense of foot-dragging or whitewashing. Quite frankly, I kind of expected it, too, because I think it's very intimidating for any management body to have an outside group come in and closely evaluate the type of work you're doing. But Dr. Patel's taken a very conciliatory approach to running the board.

"He's opened up dialogues with a wide range of groups. He's willing to look at alternative approaches to solving problems. He's been a very positive force."

The task force took six months to complete its investigation and made a number of recommendations designed to help the board better carry out its mandate. Among the recommendations: increasing licensing fees, enlarging the board; prioritizing complaints, and updating the board's computer system. Dr. Patel and current members are in the process of implementing those recommendations now.

But given the often emotional issues involved, even if all the task force's suggestions could be carried out tomorrow, few expect the result would be perfect harmony between the Board of Registration and its constituencies.

In fact, perfect harmony probably means somebody is not doing the job.

"It's very confusing to be criticized from opposite poles," noted attorney Paul G. Gitlin, Vice Chairman of the board and a veteran of public service.

"My own view is that when both sides criticize you, it's the strongest indication you can get that you're doing the best job possible."

Anything less than perfect harmony can be hard on the ears, but then Dr. Patel has always been a good listener. ■

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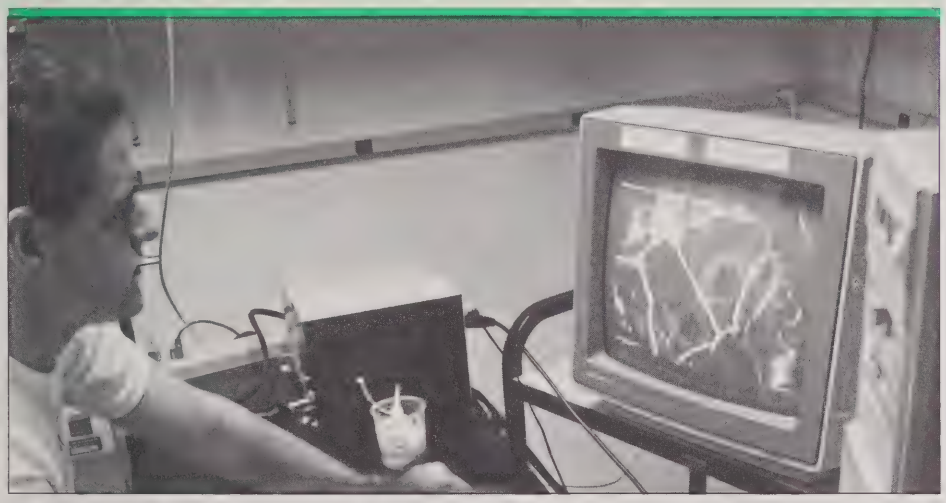
# The Artificial Liver: Closer to Reality



*Research technician Sean Sheehan examines rat liver cells preserved with a culture technique developed at the MGH.*

ALTHOUGH bionic people are still in the realm of science fiction, scientists are finding at least temporary replacements for many of the body's major organs.

Kidney dialysis led the way in the 1940s. Artificial skin — first developed at the MGH — is gaining wider application to treat burns and other ailments. The much-touted artificial heart is finding a place as a bridge device, helping patients survive until donor hearts are available for transplantation. Artificial pancreas devices, which could free diabetic patients from insulin injections, are on the drawing board.

Now an artificial replacement for the liver — the largest and one of the most complex internal organs — is becoming feasible. And researchers at the MGH are pursuing a promising discovery that is bringing such a device closer to reality.

The liver can be thought of as a massive chemical processing plant that performs tasks essential to a balanced metabolism. The liver processes glucose (sugar) and other nutrients into the forms currently needed by the body. It produces factors needed in the clotting of blood and makes bile to help digest fats. And it is the body's hazardous waste disposal facility, removing toxic substances produced by the body or ingested in foods and drugs.

The complex nature of these functions makes artificial replacement of the liver extremely difficult. Specialized nutritional support can compensate for some

*(Continued on Page 4)*

## *New Unit Addresses Policy Issues*

"THE American health care system is going to be radically different 10 years from now. Part of the MGH's responsibility is to be involved in constructive direction of that change," said David Blumenthal, MD, chief of the new MGH Health Policy Research and Development Unit.

Established last fall, the Unit is affiliated jointly with the hospital's Medical Practices Evaluation Center and its General Medicine Unit. The new program has three goals: to conduct research that will help public policy makers improve the nation's health care system; to help the MGH and other institutions anticipate and react to health policy issues; and to educate medical students and young physicians about issues that will affect their ability to serve their patients.

"David Blumenthal is one of the most exciting people in the US to address issues of health policy," said John Potts, MD, MGH Physician-in-Chief. "He combines excellent credentials as a physician with a keen mind for clear analysis of complex sociological and medical issues."

During the Unit's first few months, Dr. Blumenthal has been gathering a team of staff members interested in policy issues. Among them are five physicians: Drs. Michael Bierer, Daniel Carr, Elizabeth Mort, Albert Mully, Nancy Rigotti, and Peter Slavin.

"There is a lot of talent and interest already present here at MGH. A number of faculty members have been interested in health policy but previously had no organized focus," Dr. Blumenthal said. "I hope to attract a multidisciplinary group, including

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INSIDE

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**Relief from Hay Fever**
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EDITORIAL

# Our Shrinking Planet

OUR SHRINKING PLANET is fast changing the practice of world medicine. A quickening pace of change in medical communications began in the mid-19th century. Until then it typically took years before an advance in medicine within one nation reached a contiguous country. Just three weeks after anesthesia was successfully used at the MGH, however, England's most famous surgeon was performing an operation in London using ether.

Today with scientific publications circulated throughout much of the world, detailed information is quickly available. The facsimile machine has also considerably hastened the dissemination of medical news and shortened the path from the research laboratory to the patient's bedside. Indeed the accretion of scientific information is so immense as to sometimes confuse and even overwhelm an individual practitioner.

Contemporaneously the political structure of nations and the relationships among nations are also altering at a pace unprecedented in recent times. This too is bound to have a major impact on the practice of medicine. The dissolution of Communism and the geographic, religious, ethnic, and political fallout have already transformed the health needs of whole regions as well as individual communities. Changing weather patterns are compounding the instability.

A few years ago businessmen in India asked the MGH to mastermind the creation of a teaching hospital in Bombay. Hinduja National Hospital has now been operating for several years. In the last few weeks alone, people planning the formation of hospitals in two widely separated European countries have approached the MGH for help. Although both are planned for western Europe, the perceived need for at least one arises as the direct result of the collapse of eastern Europe. The modernization of another country in a different continent has recently resulted in an additional request for MGH expertise in establishing a hospital there.

As this was being written, a treaty was being advanced among Mexico, Canada, and the United States. The resulting revolutionary reduction in the trade barriers among those three countries could also impact health care in Mexico and probably to a lesser degree in Canada and the United States. How this treaty would impact health care can but be speculated upon. What is certain is that, whether in medicine or a hundred other fields, Planet Earth will soon be unrecognizable. ■

## — Health Policy

*(Continued from Page 1)*

social scientists as well as physicians."

The Unit's initial research projects concentrate in two areas: how physician behavior can be constructively influenced to improve the functioning of the health care system and the impact that relationships between universities and industries can have on both institutions.

"People in the federal and state governments make decisions that profoundly affect the nation's physicians and can change the health care system in very important areas," he said.

"Whether you're talking about Medicare and Medicaid, whether you're talking about changes in the way hospitals and physicians are paid — these initiatives have major implications for physicians and their patients throughout the country. Decisions need to be informed by the best possible data, and the goal of our work is to improve the information that's available."

One effort to provide this information is a recently-launched study funded by the Robert Wood Johnson Foundation. The study will use several sources of information to examine physicians' involvement with uninsured patients.

"We'll be looking at the relation of physician educational indebtedness to the willingness to provide charity care and also at the effect of state policies and the competitiveness of local health care markets on involvement with uninsured patients," he said.

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PHOTOGRAPHS: Pages 1,3,4-5 photographs, Susan McGreevey; Page 4-5 graphic, courtesy of Dr. Mehmet Toner; Page 6 painting by Freeman Finick, photographed by Brenwasser; Pages 7,8 illustrations, Arch MacInnes.

Data addressing these questions will be gathered from three sources: the Young Physicians Survey conducted in 1987 and 1991 by the Robert Wood Johnson Foundation; the annual Socioeconomic Monitoring Service survey of the American Medical Association; and the National Medical Expenditure Survey, conducted by the federal Agency for Health Care Policy and Research.

"Young physicians are particularly important because they see more uninsured patients than do older physicians," Dr. Blumenthal said. "And of course they're particularly susceptible to changes in the funding of medical education. We need to find out whether a tradeoff for reducing expenditures for medical education may be to deprive the poor of needed services."

**"Decisions need to be informed by the best possible data, and the goal of our work is to improve the information that's available."**

— David Blumenthal, MD
Chief of the new MGH Health Policy Research and Development Unit.

Another question being addressed by the study is whether patients' insurance status has an effect on clinical decision-making.

"One of our hypotheses," he said, "is that physicians may provide the uninsured with acute care services and relatively neglect preventive services. They may think, 'This patient isn't insured this year, but may be next year. I'll put off ordering a Pap smear until next year when she might be covered.' It makes sense from the short-term standpoint of protecting the patient from out-of-pocket costs, but it may not from the long-term standpoint of reducing overall societal costs."

A related question is whether insurance status affects the care-seeking patterns of patients. Past studies have demonstrated that uninsured patients get less care but have not asked whether such patients seek care less often or are denied requested care.

"If uninsured patients don't even show up at the doctor's office," Dr. Blumenthal said, "we can't rely on charity care or income-based care [a sliding scale of fees] to provide needed services. Past analyses of the National Medical Expenditures Survey — a regularly conducted survey of a representative sample of American households — have only looked at the use of care. We're going to see whether care-*seeking* behavior is influenced by insurance status."

Academic-industry relationships are becoming more important, as the government no longer provides significant annual increases in funding for medical research. Dr. Blumenthal recently received a two-year Shannon Award from the National Institutes of Health to repeat and expand on research he conducted in the early and mid-1980s. Those studies surveyed academic faculty members involved in biomedical research — both with and without industry support — and a sample of biotechnology companies.

"I think it's very interesting to look at publication rates among faculty to see whether industry involvement affects academic productivity in a measurable way," Dr. Blumenthal said.

*Dr. David Blumenthal reviews study data with Jennifer Edwards (standing) and Dr. Elizabeth Mort.*

"My past work has shown that it doesn't. But we haven't looked at relationships like equity holding by university faculty, which is an issue of some controversy."

Other questions he hopes to explore include levels of secrecy among university faculty who are and are not involved in industrial arrangements, whether such arrangements are associated with financial gain for faculty members or the universities, and whether biotechnology companies that are involved with universities are more productive and profitable than those that are not.

While acknowledging the sensitivity of these issues, Dr. Blumenthal stresses their importance: "I don't think universities are going to have anything to worry about. For the most part they've conducted themselves very carefully and scrupulously.

"But if university-industry relations are truly changing the biological research enterprise in ways that are potentially negative," he adds, "then it is incumbent on the managers of that research enterprise to try and ameliorate the situation."

An Assistant Professor of Medicine and Social Medicine at Harvard Medical School, Dr. Blumenthal is a graduate of HMS and also received a master's in public policy from Harvard's Kennedy School of Government. During a break from his medical residency at the MGH, he worked for Senator Edward Kennedy as a member of the Senate Subcommittee on Health and Scientific Research.

After completing his residency he divided his time between teaching at the Kennedy School and patient care at the MGH until 1987, when he became a senior vice president at Brigham and Women's Hospital. There he was responsible for areas including commercialization of research; potential conflicts of interest; legal affairs; and quality management. He also served as chief health policy advisor to the 1988 Dukakis presidential campaign. ■

## —Artificial Liver

*(Continued from Page 1)*

functions; clotting factors can be added. But for processing and removal of toxic substances, nothing can yet replace the liver cell, also called the hepatocyte.

Today the only option for people with liver failure is a transplant. But a partially damaged liver has a remarkable ability to regenerate, which makes it possible for a parent to donate a portion of a healthy organ to a child with liver failure.

***A significant number of those who now receive transplants could recover from their illness if there were a way to replace liver function during the time it would take for their damaged livers to regenerate.***

"A key use for an artificial liver would be in cases of acute liver disease, usually due to viral hepatitis or a toxic injury such as a drug overdose," said MGH gastroenterologist James Richter, MD. The liver also could probably recover from damage caused by loss of blood in an accident.

An artificial liver could sustain someone waiting for a transplant who might otherwise die before an appropriate organ becomes available. It could remove the toxins that literally poison people with liver failure, improving their overall health and their chance of surviving the grueling transplant procedure.

At the MGH, the artificial liver research effort is lead by Ronald Tompkins, MD, PhD, and Martin Yarmush, MD, PhD. Bioengineer Mehmet Toner, PhD., joined the team two years ago.

Their goal is a device in which healthy liver cells are brought into contact with plasma (the clear, water-like component of blood) from a patient with liver failure. Under the right conditions, the liver cells could remove toxins from the plasma, which would then be returned to the patient. Such a device could also accomplish many of the liver's other functions.

Getting a supply of healthy, functioning liver cells has proven difficult, however. Scientists have not been able to induce them to regenerate in the laboratory.

In addition, simply preserving liver cells removed from human or animal donors is a problem. In the liver, the cells have a many-sided shape and are packed together like rows of bricks. Blood flows through channels above and below the rows, carrying in toxins and picking up essential proteins. Bile is secreted into channels between the "bricks" and passes into the bile ducts for storage in the gallbladder.

Liver cells preserved by standard laboratory culture methods, however, lose their specialized functions. If left in culture long enough, they are no longer identifiable as liver cells.

Four years ago, however, an important discovery was made in the Tompkins/Yarmush lab. "We had hypothesized that, because liver cells in the body are bounded on at least two sides by extracellular material, cells taken out of the body would be much more at home if this geometric relationship was maintained," said Dr. Yarmush, who is an Assistant Professor of Surgery (Immunology) at Harvard Medical School.

Pursuing this prediction, graduate student James Dunn found that liver cells maintained their normal appearance and function if placed in what is called a sandwich culture configuration: a single layer of cells between two layers of collagen gel. Collagen is a protein found in much of the body's connective tissue. (A 1992 graduate of the Harvard/M.I.T. Division of Health Sciences and Technology, Dr. Dunn is now a surgical resident at U.C.L.A.)

Dr. Tompkins said, "This simple configuration, which closely reproduces the *in vivo* [in the animal] environment of the cell, was a significant improvement. We are now trying to apply it to several possible designs for a liver replacement device."

The designs being pursued are aimed at solving another challenge: getting as many liver cells as possible into a small area while allowing space for plasma to spread between the cells.

"The liver is a very porous environment," said Dr. Toner. "There is very efficient distribution of blood between the liver cells, which is not easy to duplicate in the laboratory. We want to have the largest possible surface area of cells exposed to the plasma, otherwise you'd need a huge amount of plasma just to prime the device [to prepare it for operation]."

One idea the team is pursuing involves the use of microcarriers — tiny spheres that would be coated with a layer of cultured liver cells. Thousands of coated microcarriers would be packed into a device, like marbles in a jar, and plasma would flow around and between them.

One of the problems to be solved in making this model work is developing a special outer layer for the liver cells in the sandwich culture configuration. This layer would have to protect the cells from the friction and stress forces of moving fluids and adjoining microcarriers, while still allowing substances to pass back and forth between plasma and the liver cells.

Hollow fibers are used in another design the team is investigating. These tiny tubes would carry streams of plasma between cell-covered microcarriers suspended in a collagen gel. The fibers would be constructed of a specialized membrane allowing passage of appropriate molecules between the plasma on the inside and the liver cells on the outside.

A third concept involves micropatterning — the kind of microscopic etching technique used to make silicon chips. "There's a potential for transferring a pattern very similar to that of the normal liver onto a plate and seeding cells to produce a natural microscopic structure," said Dr. Tompkins, who is also Chief of Trauma and Burn Services at the MGH and an Assistant Professor of Surgery at Harvard Medical School.

These patterns would be formed by alternating two kinds of surfaces: one that liver cells will adhere to and one that they will not. The nonadherent surfaces would form microscopic channels carrying plasma to the cells stuck to the adherent surfaces.

Dr. Toner explained, "We are in the process of understanding the right conditions for these surfaces, testing them, and seeing which will give us the most surface area in the smallest volume."

Whichever design proves most efficient in reproducing liver function, it will need to be supplied with liver cells in the sandwich culture. The MGH team also is exploring two avenues toward improving the supply of cells: better understanding the process of preserving cells by freezing and solving the mysteries of liver regeneration.

"Freezing liver cells is not a simple, straightforward process," Dr. Tompkins said. "If you don't do it right you'll kill most of them, and those that survive may be damaged and release toxic products of their own."

Dr. Toner, who has a major role in the freezing project, explained that just the right balance of refrigeration and dehydration is essential. If water inside the cell freezes, the cell will die. But if there is not enough water in the cell, it will be damaged by excessive dehydration.

"We have actually demonstrated that cells in the collagen-gel sandwich are more resistant to freezing damage," he said. "Now we need to find out the biological and physical reasons for this greater stability."

In studying liver regeneration the investigators are trying to get around a central problem. Regeneration only happens inside the animal, but that is where it is most difficult to observe.

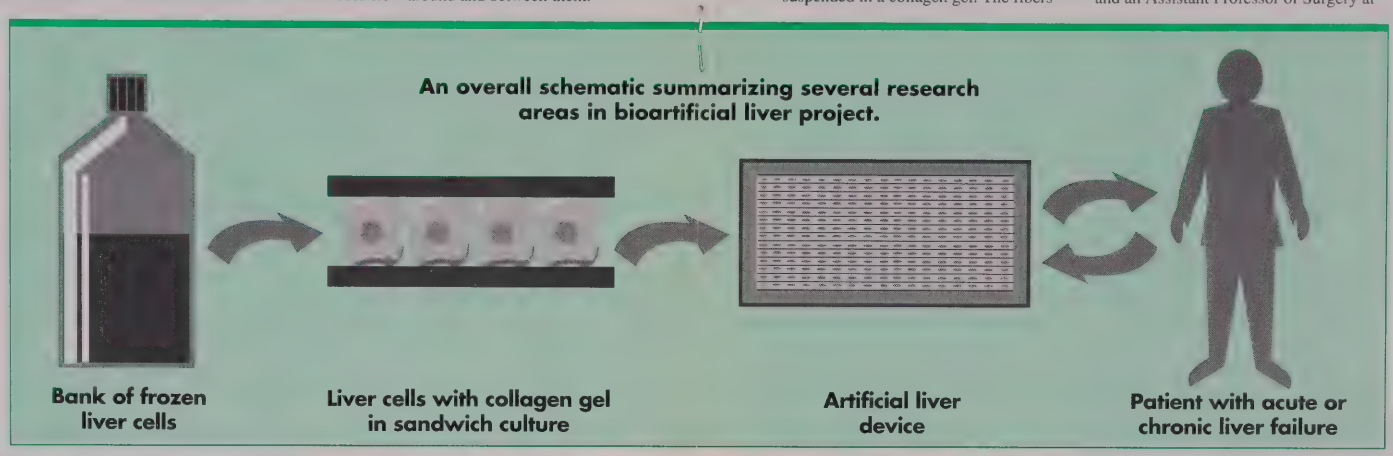
They plan to construct a small version of one of the artificial liver devices and connect it to an experimental animal from which the liver has been partially removed. Using a microscopic "window" into the device, they hope to examine the cultured cells for signs of regeneration.

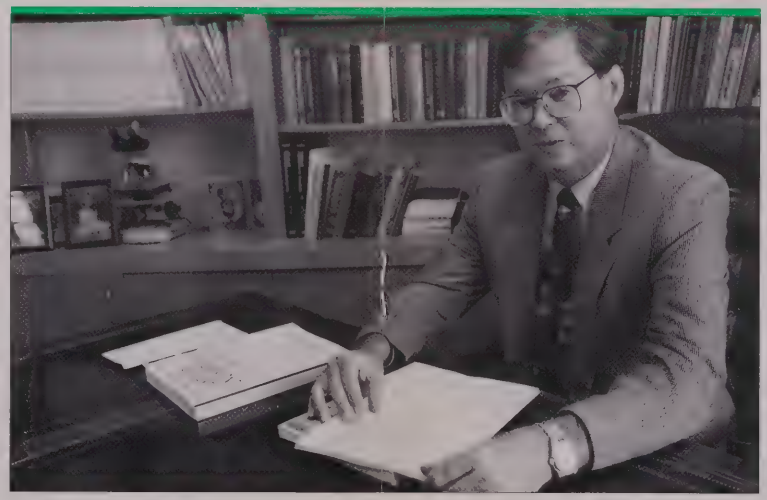
"The animal would be producing the metabolic signals that induce liver regeneration," said Dr. Toner, who is an Assistant Professor of Surgery at Harvard Medical School. "We want to expose the cultured cells to the *in vivo* chemical conditions observed during regeneration. If we see regeneration in this device, then we can examine the process on a cellular level to find out why we can't get cell growth in a lab dish."

Until the regeneration problem is solved, cells for any artificial liver device can only come from either human or animal donors. Some of the cells employed in the research project have come from humans — from healthy liver tissue removed along with a tumor or from donor livers that were not eventually transplanted. But animal tissues are being used in most of the studies, and animals may eventually be the source for cells employed in an artificial liver device.

Dr. Tompkins explained that the filter separating a patient's plasma from the bloodstream would prevent human immune system components like antibodies from coming into contact with animal liver cells. In addition, patients who would require artificial liver treatment would probably be too ill to mount a normal immune response.

"There might be some reaction to the proteins produced by these cells that are delivered back into the circulation," he said. "But many animal proteins, such as insulin, are very well tolerated. This is an unusual, immune-protected environment. Immune tolerance may not be the most difficult problem." ■


An overall schematic summarizing several research areas in bioartificial liver project.
Bank of frozen liver cells
Liver cells with collagen gel in sandwich culture
Artificial liver device
Patient with acute or chronic liver failure



*Dr. Ronald Tompkins*

# *Dr. Churchill's 'Wandering Year' Helped Set His Career's Course*

FOR Edward D. Churchill — one of this century's pioneers in thoracic surgery and an historic figure at the MGH — the year he spent in Europe as a Moseley Travelling Fellow was a life- and career-defining experience. His account of that year is the centerpiece of *Wanderjahr: The Education of a Surgeon*, published by the Countway Medical Library at Harvard Medical School.

The book is edited and annotated by J. Gordon Scannell, MD, MGH senior surgeon and a long-time colleague of Dr. Churchill. A set of 1956 interviews with the noted surgeon, conducted by author Saul Benison, has been woven into an account of Dr. Churchill's 1926-27 *Wanderjahr* (a German term for a "wandering year," spent traveling before settling down to a profession).

In his introduction, Dr. Scannell describes how the young Harvard Medical School graduate longed to pursue scientific research along with clinical surgery. But the conservative, technically centered attitudes of the MGH surgical staff, which consisted of part-time visiting surgeons in the early 1920s, frustrated that desire.

An opportunity to work in the physiology lab of Dr. Cecil Drinker at Harvard School of Public Health allowed Dr. Churchill to pursue an interest in the lung. Perhaps as a result of that association, the University of Pennsylvania, Dr. Drinker's alma mater, offered Dr. Churchill a research professorship.

He turned down the offer, however, and instead accepted the Moseley Travelling Fellowship, awarded by Harvard Medical School to promising graduates wanting to spend a year or more training in Europe, still regarded as the center of medical research and education.

"By present day standards my *Wanderjahr* as a Moseley Fellow was strangely unorganized," Dr. Churchill said. "I intended to visit a number of European clinics to see what opportunities for work in experimental surgery were available, but I planned no itinerary. My primary objective was to gain experience in the laboratory approach."

*This 1962 painting, made in honor of his retirement, includes many noted physicians who trained under Dr. Edward Churchill at the MGH. Pictured are (from left): Dr. Henry Edmunds (rear), Dr. Edwin Salzman (front), Dr. Ronald Malt, Dr. Churchill, Dr. Anthony Monaco, Dr. John Constable, Dr. Harold Urschel, and Dr. Charles Huggins.*

His success in meeting this objective was mixed. Several of the noted surgeons he encountered did little or no laboratory research. But the experiences he recounted hint at lessons that were to shape his future career. British surgeon Blair Bell's use of lead to treat cancer patients may have been medically wrong, but his compassion for and empathy with his patients made a strong impression on Dr. Churchill.

He spent much of his time on the continent in the German cities of Berlin, Munich, Heidelberg, and Hamburg — formerly major centers of learning now declining in the wake of Germany's defeat in the first war.

Dr. Churchill was struck by the tendency of German physicians to regard their patients "merely as clinical material" and was shocked by the "intellectual docility" of young surgeons who accepted the pronouncements of their masters without question or criticism.

Many experiences, however, were positive. Through observation of the work of Dr. Ernst Sauerbruch in Munich, he said, "I saw for the first time that thoracic surgery was possible; that is, thoracic surgery as a bold and planned undertaking."

In Copenhagen he had an opportunity to work in the physiology lab of Nobel Laureate August Krogh. Exposure to the thoracic surgical techniques of Professor Ludolph Brauer in Hamburg sparked many ideas that Dr. Churchill would pursue during his later career. While he did not hesitate to comment on the limitations of the surgical luminaries he visited, he acknowledged what he learned from each of them.

Dr. Scannell's epilogue describes the illustrious career Dr. Churchill resumed after his return: his development of many innovative surgical techniques, his appointment as John Homans Professor and Chief of the West Surgical Service at the age of 35 (he eventually headed both the East and West Services), and his leadership in shaping and transforming the MGH surgical residency program.

A major influence on many of today's leading surgeons, Dr. Churchill retired in 1961 and died in 1972. In summing up the man's approach to his profession, Dr. Scannell quoted from Dr. Churchill's 1947 address to the American Surgical Society.

"In times of change there is need for wisdom both in the external social order and within the profession . . . By maintaining the ancient bond with humanity itself through charity — the desire to relieve suffering for its own sake — surgery need not fear change if civilization itself survives." ■

# New Treatments Offer Relief for Hay Fever Miseries

**Summer's end brings cooler days, the first hints of autumn foliage, and back-to-school sales. It also brings sniffles, sneezes, and itchy, red eyes to millions who suffer from hay fever — properly termed allergic rhinitis.**

MANY THINK of this time of year as "hay fever season" and blame ragweed pollen for their misery. They may be right, but other weeds can contribute to the late-summer rise in the pollen count.

There also are those who suffer most in the spring, when trees send their pollens adrift on the breeze. This year's tree pollens were particularly abundant — reaching levels six times greater than those usually considered "severe" — because late-arriving warm weather caused many different species to release their pollens at the same time. Grass pollens, prominent in early summer, are culprits for others.

No matter the specific source of the problem, people with allergic rhinitis share two features that lead to their common symptoms — an immune system that makes lots of a particular kind of antibody (a specialized molecule that recognizes foreign proteins in the body) and an increased sensitivity to any nasal irritation.

"It's normal for your nose to react to irritation by becoming blocked; that's what happens when you get a cold or if you inhale too much dust," said MGH allergist Martin Ostro, MD. "Some people, however, have a much lower threshold for irritation. They may have symptoms if one person is smoking in an area or even if they walk into an air conditioned room on a hot day."

The "allergic" component of the syndrome is provided by the immune system. A particular kind of antibody — called IgE — is responsible for the allergic reaction. IgE antibodies interact with mast cells, specialized white blood cells that line the nasal passages, the tubes leading to the lungs, and the digestive system. When activated, mast cells release chemicals called mediators — the most prominent of which is histamine — that induce the allegic reaction.

Dr. Ostro explained, "When people with allergies first encounter ragweed pollen, for example, their bodies respond by producing IgE antibodies to ragweed. Non-allergic people do not produce these particular antibodies. Upon reexposure to ragweed, the pollen combines with IgE antibodies on the surface of mast cells, which triggers the release of mediators like histamine. It is these mediators, especially histamine, that bring about the typical allergic symptoms of running nose, nasal congestion, and sneezing."

So what to do when one is on the receiving end of this allergic assault? Many people find relief through over-the-counter medications, mostly antihistamines that block the activity of histamine released from mast cells. But nonprescription antihistamines often cause drowsiness,

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## —Allergy Relief

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and for some they just don't work.

In the past few years, a new family of nonsedating antihistamines has emerged. Two varieties now are available by prescription: terfenadine (Seldane) and astemizole (Hismanal). While they have become popular among allergy sufferers, recent FDA warnings raised concerns about their safety.

"The side effects the FDA warned about are not a new phenomenon," Dr. Ostro said. "All antihistamines can cause arrhythmias [irregular heart beat] if taken in excessive amounts."

The FDA cautioned against use of these drugs by people with liver disease and against prescribing terfenadine in combination with medications known to affect liver function — antibiotics like erythromycin and an antifungal drug called ketoconazole (Nizoral). Because the liver plays a major role in breaking down drugs in the body, anything that reduces that organ's function would cause levels of a medication to build up, producing the effect of an overdose.

"Some people may have been overdosing on these drugs in the mistaken belief that taking extra pills would make them work faster or better," said Dr. Ostro. "With classic antihistamines if you took too many tablets, you'd fall asleep. Because these new drugs are nonsedating, people may take four or five tablets and end up with an irregular heartbeat.

"People who do not have liver disease, are not taking the previously mentioned drugs, and do not exceed the recommended dosage should not have problems with arrhythmias," he added.

Other prescription treatments for hay fever sufferers include nasal sprays with corticosteroids (drugs that supress the inflammatory response) or with cromolyn, a medication that keeps mast cells from releasing the chemicals that induce the allergic reaction.

"The advantage of inhaled nasal steroids is that they act directly on the lining of the nose, decreasing inflammation and shrinking swollen membranes. In adults they're not absorbed into the body. They've been shown to be very effective and very safe. Cromolyn seems to somehow stablize the mast cells, preventing the release of the chemicals that cause inflammation," Dr. Ostro said.

Another option available for those with persistent allergy symptoms is skin testing to determine the specific allergen (foreign substance causing the allergic reaction) responsible for producing their symptoms.

The test involves placing tiny amounts of common allergens on the skin and pricking the skin with a needle. Inflammation at the site of a specific antigen shows the presence of IgE antibodies to that substance. Knowing which allergen (or allergens) is responsible, said Dr. Ostro, "may allow the doctor to recommend specific environmental control measures to minimize contact with the offending substance."

If it is not possible to avoid the allergens, or if symptoms persist despite avoidance efforts and medications, immunotherapy or "allergy shots" can be considered.

"Immunotherapy decreases the body's ability to make IgE antibodies," Dr. Ostro explained. "People receive increasing weekly doses of the allergens over about 20 weeks. The maximum dose achieved is then continued on a monthly basis for at least three years."

Dr. Ostro added that with the newer treatments available to control symptoms, immunotherapy is needed less frequently. The treatment's safety and effectiveness have been long established in studies conducted by numerous investigators, including Dr. Francis Lowell, former head of the MGH Allergy Unit, and Dr. William Franklin, an MGH allergist.

"People who don't have allergies tend to think they're nothing much," Dr. Ostro said. "But just recall how you feel when you have a severe cold: your head is stuffed up, you can't concentrate, you're functioning far less than your best. You can feel like that and worse with hay fever. People with allergic nasal disease should know that their physician can offer several different treatments to decrease their symptoms." ■

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# MRI — Pushing the Limits of a Technology

*(The first of two articles)*

MAGNETIC resonance imaging (MRI) is being transformed from a slow, still-picture technology to one capable of producing actual motion pictures of changes in such organs as the heart and brain. MGH researchers are leading the way in the remarkable advances being made in one of medicine's most versatile imaging techniques.

Scientists at the MGH-NMR Center in Charlestown were the first to produce MRI images showing changes in the brain occurring in response to sensory activity. One such MGH image of a brain responding to a flashing light appeared on the cover of the November 1991 issue of *Science*.

The MGH team then refined their techniques to produce the first continuous, real-time images of the brain at work. ***These accomplishments are already revolutionizing understanding of how the brain works and should greatly reduce the hazards of brain surgery.***

The advances were made possible by new equipment that reduces from several minutes to fractions of a second the time required to create an MR image. Instascan — the fast MRI scanner made by Advanced NMR Systems of Wilmington, Mass. — was developed and tested in close cooperation with MGH specialists.

NMR — nuclear magnetic resonance — is an umbrella term for several related technologies utilizing the magnetic properties of atoms. The signal produced in NMR disappears very quickly, in a few tenths of a second. Previously it was not possible to record in a single collection all the information needed to construct a three-dimensional MR image. Hundreds of readings were necessary to compile the required data, a process that took from a few minutes to an hour.

As a result, although MRI produced images of intricate detail unrivaled by any other technology, it could not show what was happening at a particular moment. The images showed the structure of an organ but could not record function or activity. The motion of a beating heart, an expanding lung, or of patients themselves compromised image quality.

The Instascan device is able to collect enough data to create an image in a single

*(Continued on Page 4)*

## *A Source of Reassurance*

WHEN Mary Jo Covey found out that she was pregnant last fall, she was ecstatic. And she was terrified. Because for the past year — including the first six weeks of this pregnancy — she had been taking clonazepam (Klonopin), an antianxiety drug to treat the panic attacks that began several years before.

As a nurse, Ms. Covey knew that the first weeks of a pregnancy were the crucial time of organ formation, when the embryo is most vulnerable to drugs that might cause birth defects.

"On one hand, I was afraid to stop taking a drug that I needed. On the other, I was worried about effects on the child. I felt totally out of control," she said.

Ms. Covey's psychiatrist, Rebecca Neal, MD, is a member of the MGH staff. She told her patient of a special MGH program designed to help women in the same position: those being treated with antidepressant or antianxiety drugs who either become pregnant or would like to have children.

The Perinatal Clinical Psychiatry Research Program is a special service within the MGH Clinical Psychopharmacology Unit. Lee S. Cohen, MD, director of the program, explained that they are addressing a significant need, since mood and anxiety disorders are most common in women of childbearing age.

"We set up a small consultation service in the mid-1980s to help these women and their doctors weigh the risks of using drugs versus the risks posed by a possible return of their disorder."

Since that beginning, the group has

*(Continued on Page 2)*

*Mary Jo Covey and her son Brendan*

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**Compulsive Hair-Pulling**
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EDITORIAL

# To Set the Record Straight

THE HISTORY OF DISCOVERY is replete with injustices. Christopher Columbus is being honored on the 500th anniversary of his "discovery" of the new world, though many others had preceded him. Then Amerigo Vespucci, who was *not* one of Columbus's predecessors, lent his name to the new continent after the author of a book published in 1507 suggested the land be called America because Vespucci had "discovered" it.

Even 500 years after Columbus, discoveries are still misreported. When it happens in a newspaper of the quality of the *New York Times,* the facts may be distorted forever.

To set one record straight, let's examine the case of the MGH-NMR Center research team. Employing an advanced technology, the team reported a breakthrough last fall in the use of MRI, a powerful magnetic diagnostic tool, to show for the first time a detailed image of a human brain reacting to a physical stimulus. The image, appearing on the cover of America's leading scientific journal, *Science,* showed portions of a person's brain "lighted up" in response to the individual looking at a flashing light.

Aside from the sheer drama of the event, it marked the beginning of a new era in the study of the brain. The process of mapping a brain into *precise* sections according to their function was underway. In the not-too-distant future could lie major improvements in diagnosis and eventually treatment or cure of neurologic, and even psychiatric, disorders. The *New York Times* received a copy of the *Science* article along with releases from both the journal and the MGH. Nothing appeared in the *New York Times.* Twelve days later, the newspaper ran a front-page article on an elegant study made using a different imaging device called PET to light portions of the brain in action. There was no mention of the recent *Science* magazine article or the MGH research.

The researchers here were too busy carrying out exciting followups of their original flashing-light experiments to take more than passing notice. This past June 15, the scientists published in *Proceedings of the National Academy of Science* another amazing advance. They reported creating the first motion pictures of the brain functioning. And they achieved these without even using invasive contrast dye, heretofore needed to make certain types of MR images clear. This time the *New York Times* was interested. The *Times* published a long article about the feat on the science page. However, the *Times* reported it as a series of almost simultaneous ***independent*** advances by a number of different institutions. One of them mentioned briefly was the MGH.

What the article failed to note was the following: The MGH did the research first, then reported their results — and *how* they achieved them — to the tenth annual meeting of the Society of Magnetic Resonance in Medicine in August of 1991 in San Francisco. Investigators attending from other institutions were so excited that they couldn't wait to return to their own laboratories to duplicate the experiments. And duplicate them they did, thus ***validating*** the original MGH work. Some of those other researchers, after being credited by the *Times* with independent, almost simultaneous findings, telephoned the MGH group to say so. They were also embarrassed that their own names appeared in the story but not that of the young MGH scientist, Kenneth K. Kwong, PhD. The *Times* never even acknowledged receiving an MGH letter pointing out the newspaper's errors — there were several — and taking pains to credit other scientific institutions which have also made important contributions in the field.

The MGH scientists are philosophical about the events. In the long run the medical advances resulting from their work will benefit humans in ways one cannot now even predict. Still, everyone who works hard to create something enjoys a little recognition now and then. Especially in one of the world's great newspapers, which so often does sense what is trailblazing. ■

## — Reassurance

*(Continued from Page 1)*

seen more than 1,000 patients — both from the MGH psychiatry clinic and on referral from obstetricians at other hospitals — providing a service available at only one or two other centers in the country. Recently the MGH group began addressing two related problems in women's health: postpartum depression and premenstrual syndrome (PMS).

"It has been traditional to avoid any drugs during the first three months of pregnancy, because that's when organs are formed," Dr. Cohen said. "However, discontinuing medications can be risky as well. Taking a patient off antidepressants may result in a relapse. If she becomes dysfunctional — not eating well, not following prenatal care guidelines — that can have an adverse effect on the pregnancy."

During its first years, the program largely served as an information and consultation resource, providing access to the latest data about commonly prescribed psychotropic drugs (drugs affecting mood and other mental states). More recently, the group has received National Institute of Mental Health funding to add a research component.

Now the MGH specialists are following women like Ms. Covey throughout their pregnancies and during the postpartum (after birth) period, both to provide a continuing source of information for obstetricians and to gather information about which women do well and which have problems during their pregnancies.

Correlating the eventual outcomes with

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PHOTOGRAPHS: Pages 1, 3, 5 photographs, Susan McGreevey; Pages 4-5 MR images, courtesy of Dr. Kenneth Kwong; Page 6, illustration, Arch MacInnes.

patients' specific psychiatric illnesses, their past histories (including previous attempts to discontinue medication), and the treatments should help refine and improve the care of future patients.

Although discontinuing all drugs during pregnancy is the ideal, it is frequently determined that continuing medication — or returning to medication if symptoms recur — is the safest course.

"Fortunately," Dr. Cohen said, "the information we have regarding the older tricyclic antidepressants, benzodiazepines [antianxiety drugs], and even lithium [used to treat manic-depressive disorder] suggests that the risks of using those agents during pregnancy is less than previously estimated."

Dr. Cohen, who also is an assistant professor of psychiatry at Harvard Medical School, looks forward to collaborating with the new obstetric service that will be offered through the MGH-Vincent Memorial Gynecology Service, starting late in 1994. He noted that the patients the perinatal psychiatry group works with are highly motivated and very grateful for the guidance provided by the service.

*Dr. Deborah Sichel and Dr. Lee Cohen*

In Ms. Covey's case, Dr. Cohen assured her that the risk posed by her medication was slight. He acted as a liaison with her obstetric group, providing them with information about the medication as well.

When they decided to attempt drug discontinuation later in Ms. Covey's pregnancy, Dr. Cohen encouraged her to see a behavioral psychologist to learn relaxation techniques such as self-hypnosis that would both help avoid panic attacks and make labor and delivery easier.

"I don't think anyone could totally take away the worry of birth defects," she says. "You'd worry if you even had a glass of wine. But it was very consoling to have them telling me it was OK to take this medication if I needed it. And when I decided to go off the drug, they were very supportive. I'm really grateful for that."

Her healthy son, Brendan, was born in June; and Ms. Covey has continued to stay off medication. "The techniques I learned have been really helpful, it's amazing. But the Klonopin is a backup I'll always have."

Some people, Dr. Cohen acknowledged, may question the wisdom of childbearing for women with psychiatric disorders. But that concern "speaks more to the stigma of mental illness than to a real issue.

"Most of the women we see are doing very well — functioning well in their work and in their home lives. In more than 1,000 patients I can think of only one or two whose illnesses were so grave that I questioned whether they should be parents at all."

The MGH group's work in treating psychiatric illness during pregnancy led naturally to an interest in postpartum depression. While a period of feeling let down or "blue" may seem a normal reaction to the stresses of parenthood, as many as 10 percent of new mothers have symptoms serious enough to be classified as mood disorder.

Deborah Sichel, MD, a nationally known specialist in postpartum depression, joined the perinatal psychiatry program in 1990. She noted that educating obstetricians to recognize postpartum depression and to identify women at risk are essential.

"Women known to have had episodes of even mild depression or other mood disorders and those with a family history of such problems are definitely at risk," she said.

Prevention of postpartum psychiatric illness, she stressed, should start with the first prenatal visit. When risk factors are identified, the woman can be followed closely and treatment initiated as soon as significant symptoms occur.

In addition, the personal support any new mother needs — from her husband, family, friends — can be evaluated before delivery to smooth the adjustment period.

The risk of relapse in women who had serious postpartum depression with a previous pregnancy is high — perhaps 50 to 75 percent. If an antidepressant medication succeeded with the earlier episode, the same drug is started right after delivery to prevent recurrence.

While this strategy is successful for many at-risk women, some still have at least a brief period of serious depression. To help these patients, Dr. Sichel and her colleagues have begun studying the possible use of estrogen to prevent relapse in women with a history of postpartum depression.

While occasionally women referred to the MGH clinic are found simply to be overwhelmed with family demands, Dr. Sichel stressed that the patients they treat are seriously ill. "It is essential to differentiate women with mild symptoms, who certainly deserve support and help, from those with major depression. Frequently physicians have not made that distinction.

"Some physicians think it's normal for a postpartum woman to be depressed," she added. "That's simply not true."

Treatment of premenstrual syndrome (PMS) also begins with accurate diagnosis. Dr. Cohen explained: "If we were to place an ad in the paper asking for women with PMS and 100 patients came in, roughly 70 to 80 percent would really have a mood or anxiety disorder.

"But there also is a distinct group of women not meeting criteria for these disorders who experience symptoms — such as irritability, mood swings, anxiety, and headaches — so severe as to interfere with normal activities."

For these patients, Dr. Cohen's group starts with simple strategies such as closely documenting the nature and timing of symptoms and keeping track of foods eaten. Restricting caffeine intake, following a balanced moderate diet, and daily aerobic exercise seem to help up to 70 percent of such women. For the others, short-term use of antianxiety or antidepressant medications may be useful.

In their research into PMS, the perinatal psychiatry group plans to collaborate with researchers in the MGH-Vincent Gynecology Service who will be investigating the syndrome's biochemical basis. Led by Raja Sayegh, MD, that group will study the relation between diet and PMS-associated mood changes, specifically whether a high-carbohydrate diet could have a positive effect.

"What we are able to offer the gynecology researchers," said Dr. Cohen, "is a group of patients who have been carefully evaluated and whose diagnosis of PMS is clear. We hope to put our heads together and look more clearly at the hormonal variables associated with this problem."

Dr. Isaac Schiff, chief of the MGH-Vincent Memorial Gynecology Service, said of the perinatal psychiatry program, "This unit can help women in a major way. In the past, many people didn't acknowledge that postpartum depression and PMS were real conditions.

"The group's work has the potential to come up with real solutions to these problems, helping us meet our goal of dealing with all aspects of women's health care." ■

# — MRI — Pushing the Limits of a Technology

*(Continued from Page 1)*

reading. A unit was installed in 1990 on a research magnet at the MGH-NMR Center. Mark S. Cohen, PhD, Director of the High-Speed Imaging Laboratory, said that since then, "MGH investigators have been extraordinarily creative about finding useful things to do with this device. We have opened vast areas of research, extending well beyond clinical medicine."

The spectacular successes in brain imaging result from a fortunate convergence of several avenues of research pursued at the MGH. Studies into the use of contrast agents to enhance MR images have been particularly fruitful.

Contrast agents — materials that, once injected into the body, can be seen by an imaging procedure — are not needed in standard MRI examinations. They can, however, help get around some of the technology's limitations.

Bruce R. Rosen, MD, PhD, MGH Director of Clinical NMR, explained, "One of the problems with MRI has been that, although it's very good at spotting an abnormality, it's less good at telling what that abnormality is — a tumor, a cyst, or something else."

In the brain, use of MRI contrast agents can show whether there is a leak in the blood-brain barrier, a layer in the blood vessels that normally prevents chemicals from passing into and out of the brain. Disruption of this barrier is often associated with very malignant brain tumors. Slow-growing tumors, which may look no different on a standard MRI, cause little barrier breakdown.

"By using the contrast agent, we can determine whether a lesion is, in fact, a tumor and whether it is a fast-growing tumor that should be treated aggressively," Dr. Rosen said.

Dr. Rosen and his colleagues, Arno Villringer, MD, and Jack Belliveau, MD, soon realized that contrast agents had a potential for revealing more significant information. Standard technique creates an image after the contrast agent is evenly distributed throughout the bloodstream and only shows the architecture of the vascular system.

However, right after a contrast agent is injected into the body, it passes through the circulatory system in a concentrated mass. By observing the agent's first pass through the brain, scientists could measure aspects of the blood flow into specific areas. An increase of blood flowing to a given section of the brain (the visual area, for example) follows activity of those brain cells.

But without a fast scanning technique, catching that first surge of contrast material — which only takes 10 seconds — would be impossible. "When we had both of those tools together, then we were able to look at what was actually happening in the brain as the contrast agent was being injected," Dr. Rosen said.

In a project led by Dr. Belliveau, healthy volunteers underwent contrast-enhanced MRI brain scans while wearing special goggles that alternated complete darkness with a flashing light pattern. Areas of the brain known to respond to visual signals showed clear increases in blood flow when volunteers saw the light images.

"Jack was the first to produce MR images of the activated brain," Dr. Rosen said. Such images had been produced in the past using the PET (positron emission tomography) scan — another technology pioneered at the MGH and at Barnes Hospital in St. Louis.

Images produced by PET, however, are much less detailed than those available by MRI. They are less accurate in pinpointing the exact location and timing of observed brain activity. In addition, PET studies must be done at institutions possessing a cyclotron, a device usually found only at major research centers.

Kenneth K. Kwong, PhD, a research fellow in Dr. Rosen's group, was inspired by the MR brain images to try a much more difficult step — imaging brain activation without contrast agents. He planned to take advantage of two properties of MRI for imaging the vascular system.

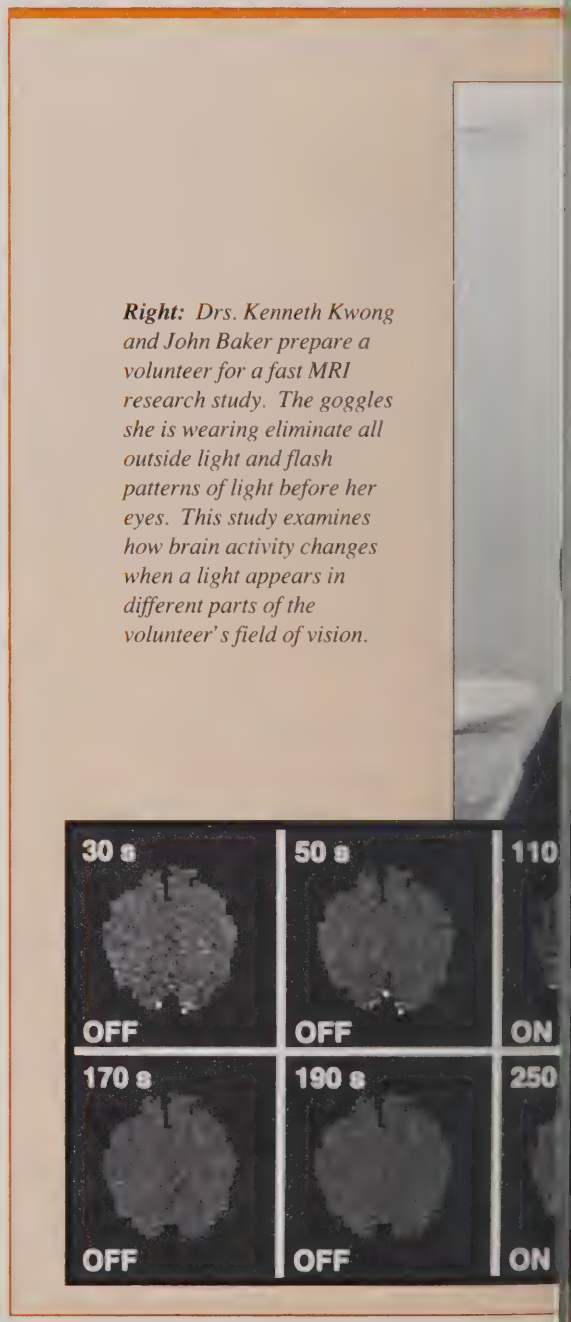
The first is a difference in the MRI signal of blood that was full of oxygen from that received from oxygen-depleted blood, a discovery made more than ten years ago by Keith R. Thulborn, MD, PhD, of the MGH.

The second is the ability to visualize blood flow, the amount of blood passing through a vessel, developed through the work of Van Wedeen, MD. Dr. Wedeen pioneered MR angiography (imaging of the blood vessels) at the MGH in the early 1980s.

The changes in blood flow and oxygenation that accompany brain activation are quite subtle. It was far from certain that they could be detected by contrast-free MRI. Dr. Kwong and his colleagues were quite surprised by the high quality of the images they obtained with the same sort of light exposure techniques used in the contrast agent experiments.

Because these readings did not depend on catching a short-lived surge of contrast agent, a sequence of scans taken as fast as once every 50 thousandths of a second (50 milliseconds) could be collected over several minutes. These were then combined into a motion picture showing on-and-off activation of the brain's visual center in response to flashing lights.

***Not only were these the first moving images of brain activation, they also were the first images of brain function***




***Right:*** *Drs. Kenneth Kwong and John Baker prepare a volunteer for a fast MRI research study. The goggles she is wearing eliminate all outside light and flash patterns of light before her eyes. This study examines how brain activity changes when a light appears in different parts of the volunteer's field of vision.*

***produced completely noninvasively, without injecting either contrast agents or radioactive chemicals.***

Dr. Kwong demonstrated his imaging technique at the Society of Magnetic Resonance in Medicine conference in August 1991. The presentation in San Francisco generated such intense interest that more than 20 institutions around the world have duplicated his blood oxygenation experiments.

***Subsequent MGH experiments have showed sequences of brain activation in response to sounds, to the volunteer's tapping a finger, and even have showed activity on a single side when a signal was seen to the right or left of a volunteer's field of vision.***

"Through Ken's work," said Dr. Rosen, "we are now in a position to map out which parts of the brain are involved in different activities in a completely noninvasive and high-resolution sense." In addition to providing new knowledge about brain function, that ability will have important patient-care applications.

In cases of severe epilepsy that do not respond to drug therapy, the only option may be surgical removal or destruction of the brain tissue responsible for the seizures. Mapping the brain could identify the area responsible for the seizures. It also could clarify the function of surrounding tissues, helping the neurosurgeon avoid destroying critical brain activity.

Brain mapping could be even more essential in surgery for brain tumors. These growths can distort the normal brain anatomy, radically changing the position of major landmarks. "To remove brain tumors more safely, surgeons need to know the sites of functional activity for each specific patient," Dr. Rosen said.

Dr. Cohen and colleagues at Brigham and Women's Hospital also have investigated use of fast MRI to monitor laser surgery as it happens inside the brain. In animal studies, they produced MR images that precisely showed increased temperatures in tissues heated with a laser probe.

"We were able to see just a few degrees of temperature change, enough that the surgeons could very accurately control what they were doing and not be operating essentially blindly."

Beyond these specific applications, fast imaging can make MRI applicable to more patients. Thomas J. Brady, MD, Director of the MGH-NMR Center, explained, "These include patients who are uncomfortable in enclosed spaces and those who are so sick they shouldn't be kept in the magnet for the time it takes to do a regular study. We will no longer have to sedate children to keep them from moving during a scan."

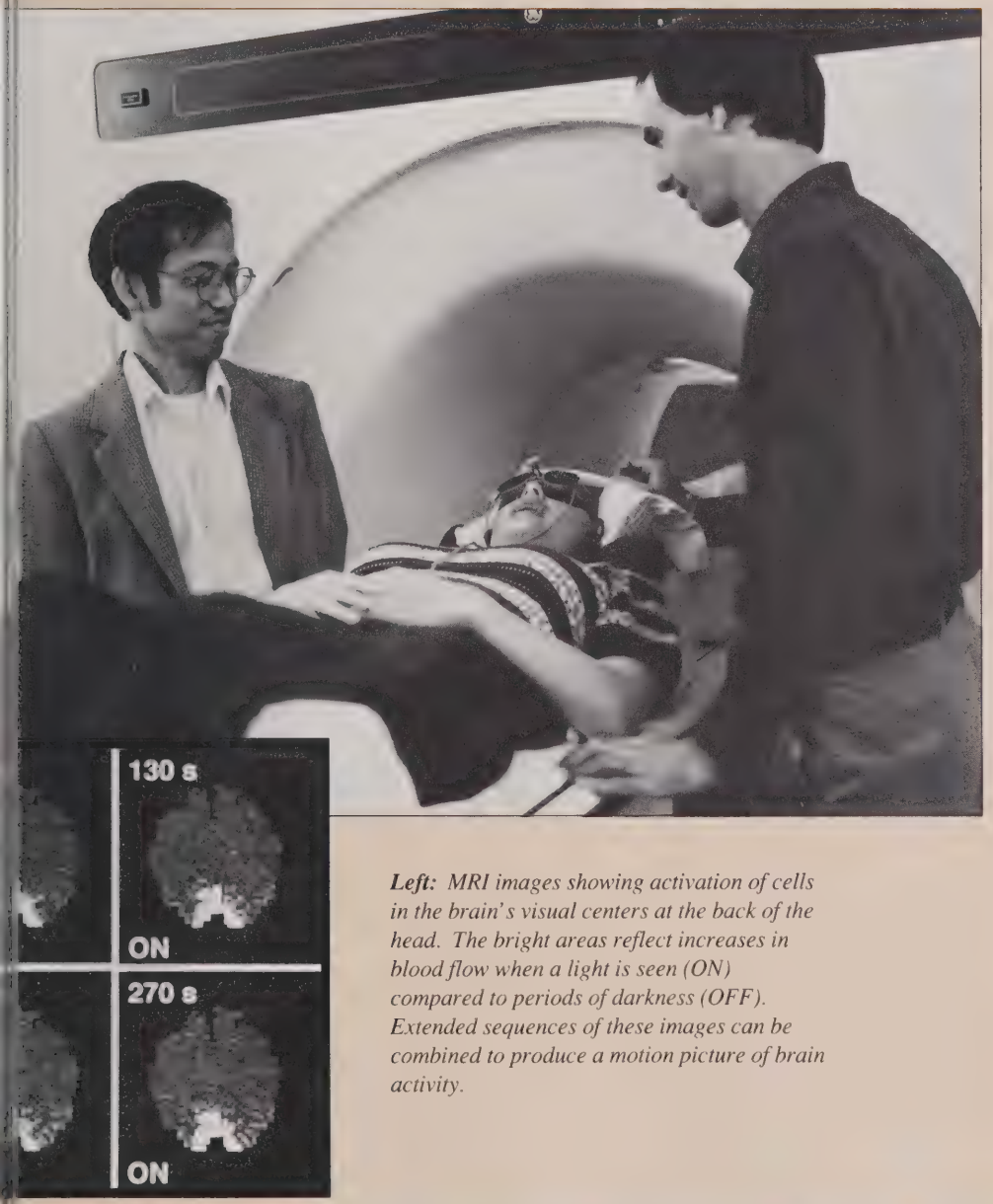
***Fast MRI also offers significant cost-saving potential. Patients with complex diagnostic needs currently may undergo several different procedures — MRI, CT scans, nuclear medicine studies. For some of them, a single fast MRI study might provide all needed data.***

With all these advantages, fast MRI promises to broaden the diagnostic uses of magnetic resonance. But the technique still has some limitations.

MRI cannot be used on patients with pacemakers or metal clips in their bodies, or those connected to life support, because the magnet would disrupt these devices. And MRI remains considerably more expensive than standard X-ray studies.

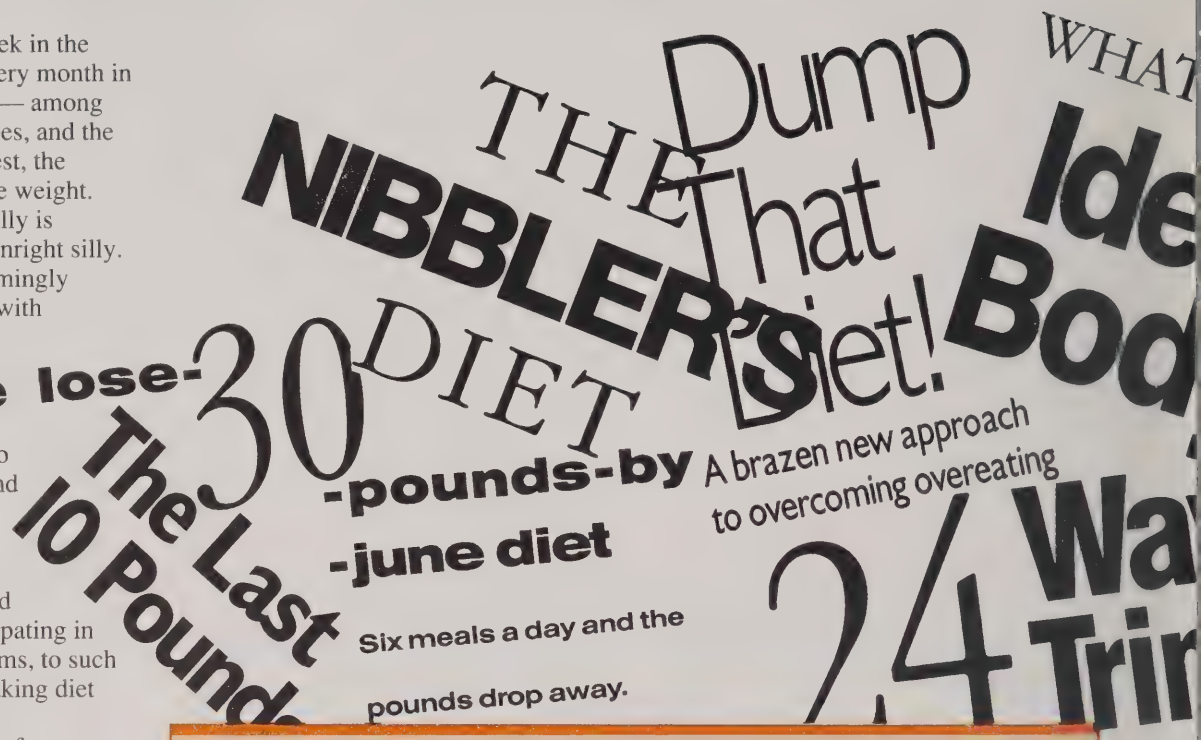
"It's a very exciting time in MRI research here at the MGH," Dr. Brady said. "We have such a wealth of talented people, and now we're developing the appropriate equipment to match those people. We're just pushing the limits of the field." ■

Editor's Note: *The next issue of* MGH News *will explore other research avenues being investigated through fast MRI and examine what the future may hold for this advancing technology.*




***Left:*** *MRI images showing activation of cells in the brain's visual centers at the back of the head. The bright areas reflect increases in blood flow when a light is seen (ON) compared to periods of darkness (OFF). Extended sequences of these images can be combined to produce a motion picture of brain activity.*

# Finding Success at Losing Weight




It's INEVITABLE. Every week in the supermarket tabloids, every month in the women's magazines — among the fashion tips, the horoscopes, and the gossip can be found the newest, the easiest, the fastest way to lose weight.

Sometimes the advice actually is sensible; sometimes it is downright silly. But it always reflects the seemingly endless American obsession with controlling or losing weight.

Earlier this year a National Institutes of Health conference reported that at any time up to 40 percent of adult women and 24 percent of adult men are trying to lose weight. The methods they use range from cutting calories consumed and increasing exercise, to participating in organized weight loss programs, to such drastic practices as fasting, taking diet pills, or inducing vomiting.

Despite these efforts, the conference reported that many fail to reach their weight-loss goals, and most who do lose gain some or all of the pounds back eventually.

Why such a dismal success rate? The answers are not yet clear. The most probable causes include unrealistic expectations, returning to old habits after a short-term success, and relying on diets that would be impossible to continue following.

Lillian Sonnenberg, DSc, RD, is Manager of Ambulatory Nutrition Services at the MGH. She explained that many people set themselves up for failure by pursuing unreasonable weight-loss goals.

"Someone may want to lose 50 pounds she's gained since she was in college. But just as she didn't gain that weight overnight, it's not going to go away overnight. And a weight that she was 20 years ago is probably not a realistic goal for today, even though she may think that is her 'normal' weight."

What seems to be more effective is taking a graduated approach, working to lose 10 or 20 pounds, for example, at a rate of one or two pounds a week. When this is accomplished, the goal becomes maintaining that weight for as long as a year before trying for any additional loss.

Dr. Sonnenberg oversees a 12-week weight-loss program offered by the MGH Department of Dietetics called "Winning at the Losing Game." The program's

## Winning Tips for Losers

WEIGHT LOSS is long-term effort, and maintaining reduced weight requires permanent lifestyle changes. While everyone's situation is different, the following tips can at least steer most would-be losers in the right direction.

- Set yourself a reasonable goal, a loss of one or two pounds per week. This loss will be easier to maintain with less chance of adverse health effects. Remember that it is normal to gain weight as you get older.
- Concentrate less on cutting calories and more on reducing fat in your diet. Read food labels to catch hidden sources of fat. A lifelong, healthy diet should be high in complex carbohydrates — breads, rice, pasta, potatoes — and in fruits and vegetables.
- Keep a record of your current eating habits to become more aware of when and why you eat. You may be surprised at how the snacks can add up. And do not forget that alcoholic beverages are an important source of calories.
- Exercise is an essential part of any weight-loss effort. Find an activity that you enjoy and can fit into your daily routine. Jogging, bicycling, and swimming are popular aerobic exercises, but walking is an excellent way to burn calories with less risk of injury. Always check with your doctor before embarking on a new exercise program.
- A registered dietitian can help you learn healthy eating and can teach behavioral modification techniques to change habits that lead to weight gain. You may find a group program helpful, but beware of those promising large, rapid losses. It is most important to find a program or counselor that you are comfortable with.
- Losing the weight is only half the battle; keeping it off is where most people falter. Continued counseling during the maintenance period (up to a year after your weight loss) can help you stay on the winning side.
- Remember that losing weight is not easy. It takes a serious, long-term commitment. A momentary lapse is not going to ruin your effort unless you allow it to discourage you. Here again a counselor can help you keep things in perspective.

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primary messages, she said, is "diets don't work!"

One of the dietitians who runs the program, Linda Delahanty, MS, RD, explained, "When you think in terms of being 'on a diet,' somewhere in the back of your mind is the day when you're going off that diet. That really doesn't contribute to long-term success."

The MGH program takes a three-part approach to building new habits and skills to last a lifetime. Participants work with a dietitian to develop a personalized eating plan; they attend an exercise class supervised by a physical therapist; and they learn techniques to change behaviors that contribute to their weight problems.

In developing the eating plans, the dietitians focus on giving participants choice and flexibility in an individualized plan that accommodates their likes and dislikes.

Cutting down on high-fat foods is a major emphasis. "We used to think that all calories were the same," said Dr. Sonnenberg. "We knew foods that were higher in fats had more calories. Now we're finding that fat calories actually are worse for you because they're stored more readily as body fat. So the theory that a calorie is a calorie doesn't seem to be true."

In addition to the program's weekly exercise session, participants are encouraged to incorporate physical activity into their daily routines. "Long-term studies have shown that people who exercise in addition to changing their diets are the ones who really keep the weight off," Dr. Sonnenberg said.

"The key is finding an exercise you enjoy and a time that's practical for you to pursue it. If you have trouble getting out of bed in the morning, trying to go for a run or a walk before work is not going to succeed."

The behavioral component helps participants recognize situations that lead them into bad habits and attitudes that can sabotage weight-loss efforts. Dietitian Sue Cummings, MS, RD, leads the behavioral segment and said, "Each participant has his or her individual problems. We help them become aware of the areas they need to work on."

Ms. Delahanty added, "Maintaining a positive attitude is essential. If someone gets on the scale and becomes very self-critical when she hasn't lost as much as she'd like, that's very defeating. We help them become conscious of this self-talk and work to keep it positive."

The 12-week MGH program can only be an introduction to techniques that participants will need to follow, probably throughout their lives. Last year, the Ambulatory Nutrition Service began a continuing maintenance group to help graduates of the weight loss program translate what they've learned into a permanent lifestyle.

"You can't expect to change 20 or 30 years of habits in 12 weeks," said Ms. Cummings. "Simply learning about proper diet and exercise isn't enough to turn behavior around. Our maintenance program is relatively unstructured so that we can address the issues that are foremost for people right now."

There are still many unanswered questions about how and why people become overweight. Esther Jacobowitz Israel, MD, an MGH pediatric gastroenterologist, noted that both an individual's environment and hereditary factors seem to be involved.

"A relatively new theory holds that increased weight really has a biological basis, that certain people's bodies are simply more efficient at storing fat. These people will always have to work at keeping their weight down. I think that idea has a lot of credibility," she said.

But, she adds, environmental factors clearly play a major role. In work with children trying to lose weight — on both a group-program and an individual basis — efforts not including a child's entire family are usually doomed to fail.

"You have to address issues such as how food is regarded by the family, whether the child is left at home with free access to the refrigerator, and whether cookies or chips are always available in the house. It's difficult to get the whole family involved in an effort, but that's really been shown to be the only successful method."

An often unaddressed issue that can affect anyone's weight-loss success is timing. "I believe that people need three things to accomplish a weight loss," Ms. Cummings said. "They need motivation, commitment, and they need readiness.

"The best program in the world may not help you if you're in the midst of such stressful situations as a new job, new baby, or loss of a loved one," she explained. "If you aren't able to focus your energies on the weight loss effort, it becomes just another failure experience. It has to be the right time for you."

# Unravelling the Mystery of Compulsive Hair Pulling

MOST OF THEM look like anybody else. Some may wear scarves, wigs, or unusual hair styles. Others have obvious patches of thin hair or bald spots. A few are completely bald and may lack even eyebrows or eyelashes.

They have in common a disorder called trichotillomania (TTM): an overwhelming compulsion to pull out their own hair. Once thought extremely rare, TTM now appears to be much more common than previously believed.

Also becoming more apparent is the devastating psychological pain experienced by people with TTM. The shame and isolation they can feel often far exceeds the degree of visible hair loss. Many believe their lives have been controlled for decades by their compulsion and the need to hide it.

Health care professionals seeking to help individuals with TTM currently are limited by a lack of scientific information. "We're really in the Dark Ages about what causes this and how to ameliorate its effects on people," said Dr. Richard O'Sullivan, a psychiatrist studying TTM in the MGH Obsessive-Compulsive Disorders Unit.

He and several MGH colleagues are launching an effort to investigate factors related to TTM and explore possible treatment strategies. These include drugs that have been effective for patients with obsessive-compulsive disorders (OCD) and behavioral therapy techniques.

Whether or not TTM should be classified as an obsessive-compulsive disorder is itself somewhat controversial. It shares the characteristic of being a compulsive activity — one that individuals cannot keep themselves from doing. But TTM usually does not include the obsessive thoughts and fears that drive the OCD patient. (See the October 1989 issue of *MGH News* for story on OCD.)

Dr. O'Sullivan explained that there may be two basic types of TTM. One starts in early childhood, even infancy, and may be outgrown. The other begins in adolescence — usually about age 13 or 14 — and persists throughout life. The adult form appears to affect more women than men. However, that observation could be wrong; it may be that men are just less

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## — Hair Pulling

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willing to seek care for the problem.

People with TTM experience the syndrome in different ways. Hair may be pulled — usually strand by strand — from a limited area of the scalp, from the whole head, or from other parts of the body. Some have bouts of anxiety coupled with the urge to pull, feelings that subside only when the hair is pulled.

Others pull almost unconsciously, perhaps while they are reading, driving, or watching television. Many people describe a feeling of being "in a trance" or not in control of their actions.

What most with TTM share is a feeling of profound shame at this lack of control. Most go for years believing that they are the only person in the world who does this. The need to hide their behavior can become an obsession of its own.

The debilitating psychological effects can be worsened by physical complications. These can include permanent hair loss, scarring, and other skin disorders. Some of those affected bite off and swallow the hairs they pull. Masses of hair may collect in the stomach or intestines and can block the digestive system.

Theories about the reasons behind TTM are many, but scientific evidence is scanty. That the syndrome runs in families has been recently noted, which suggests that there may be biological causes.

More specifically, it has been suggested that the problem results from inappropriate activation of normal grooming impulses usually seen in animals — activities such as birds' preening their feathers or cats' licking their fur. As with OCD, scientists have focused attention on a brain chemical called serotonin, and several of the drugs which are effective in TTM are known to act on the serotonin system.

What does appear certain is that TTM is not associated with deep-seated psychological problems. The hair pulling is not an expression of an urge to harm or disfigure oneself, a realization that often comforts affected people.

In their effort to answer some of the many questions about TTM, the MGH research team hopes to investigate patterns of family inheritance, look for evidence of neurologic abnormalities, and study the disorder's relation to depression and other mood disorders.

Nancy Keuthen, PhD, a behavioral psychologist in the OCD Unit, is starting to study neuropsychological functioning in hair pulling and behavioral versus pharmacological (drug) treatment interventions. "A combination of medication and behavioral treatment has appeared to be most effective," she said. "We're hoping to get hard scientific data to back up this observation."

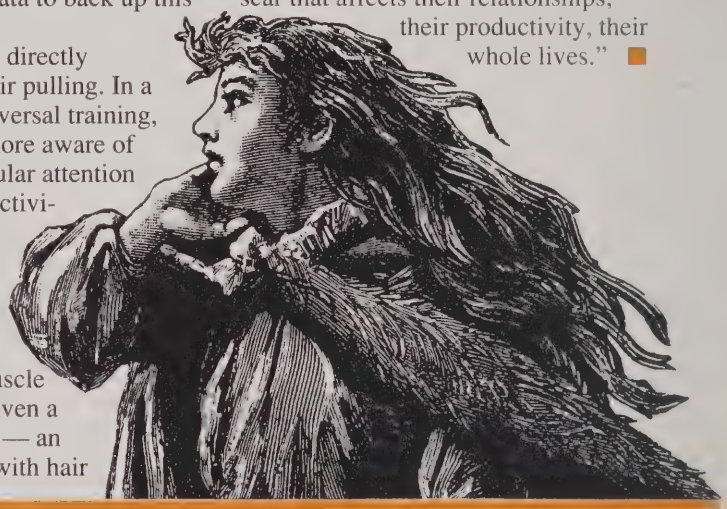
Behavioral treatment directly addresses the act of hair pulling. In a process called habit reversal training, participants become more aware of when they pull. Particular attention is paid to identifying activities or situations that may lead to pulling.

Next they learn techniques to reduce stress and anxiety, including deep breathing and muscle relaxation. They are given a "competing response" — an activity incompatible with hair pulling — to practice whenever they feel the urge to pull. Common activities include making a fist or clenching an object such as a book.

While these techniques prove helpful for many, Dr. Keuthen stressed that results do not come overnight. "If you think of how many times people have pulled their hair, that is really a potent, overlearned response. Our goal is to help them replace that response with a less disruptive behavior."

Dr. O'Sullivan agreed that, at this time, there is no easy cure. "Medication and behavioral treatment are often effective," he said. "But many people find that the process of coming in and trying to get help relieves some of their burden of shame. We also can help them rebuild their self-esteem and sense of identity, which have been compromised by trichotillomania.

"Many of these people see themselves as being 'a hair puller' every minute of the day, every day of the year. That's a scar that affects their relationships, their productivity, their whole lives." ■



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# Targeting Heart Disease Prevention

ALTHOUGH heart disease remains this country's number one killer, its grip is loosening. During the 1980s, age-adjusted death rates for heart attack dropped 30 percent; death rates for all cardiovascular diseases (including stroke) declined 23 percent.

Helping to continue and accelerate this progress is the goal of a group being organized in the MGH Cardiac Unit. The effort, under the direction of Richard C. Pasternak, MD, will bring together both new and existing hospital programs targeted toward the prevention of heart disease.

While the development of new heart disease treatments played an important role in the past decade's progress, improvements in prevention have been even more significant.

Millions are trying to live healthier lives. They have stopped smoking, changed their eating habits, and increased their physical activity. When risk factors such as high blood pressure and elevated blood cholesterol do not respond to lifestyle changes, new medications are available.

Among the most exciting developments is new scientific evidence that it may be possible to halt or even reverse the process of coronary artery disease — the buildup in the heart's blood vessels of fatty plaques that can lead to a heart attack.

But with every advance in prevention come new questions: What are the best combinations of interventions — diet, cholesterol-lowering drugs, exercise, blood pressure management — for different patients? When is cholesterol too high, when is it at a safe level, and can it actually be too low? Do results of scientific studies of men with heart disease apply equally to women?

***Dr. Pasternak believes that answering these complex questions requires a comprehensive, multidisciplinary approach — one that includes not only cardiologists and cardiac surgeons, but***
*(Continued on Page 2)*

*In the Cardiovascular Health Center, patients like Jeanne Sanders and Richard Shaughnessy — shown here with Kathy McKool, RN — work to improve their overall heart health.*

# MRI — Images of the Future

*(second of two parts)*

WITH THE development of fast magnetic resonance imaging (MRI) described in the October *MGH News*, research into novel uses for the technology has leaped forward.

New equipment partially developed at the MGH allows the creation of a detailed, three-dimensional MR image in a fraction of a second, rather than in several minutes as previously required. Thus the technique has advanced from showing only the structure of a body part to revealing details of function — what is actually happening in a portion of the brain, the heart, or other organ at a specific time.

Now MGH scientists are investigating new ways to apply MRI's abilities to the diagnosis and even treatment of a variety of conditions.

Close behind imaging of the brain (detailed in the first article of the series), imaging of the heart is a primary interest Because of its constant motion, the heart has been more resistant to conventional MR imaging than any other organ.

"There have been many technical problems in cardiac studies, and we're hoping fast imaging will resolve them," said Thomas J. Brady, MD, director of the MGH-NMR Center. (NMR is nuclear magnetic resonance, a term referring to technologies — including MRI — based on the magnetic properties of atoms).

Some of the approaches being tested in cardiac imaging involve new contrast agents, a research effort led by Ralph Weissleder, MD, PhD, director of the MR Pharmaceutical Program. These materials, visible to an imaging procedure after they are injected into the body, can be used to study cardiac function. A fast MR scan is timed to coincide with the first surge of
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EDITORIAL

## The Longterm Results Can Be Extraordinary

CARDIOLOGY stands poised to exploit the burgeoning knowledge about preventing and perhaps reversing coronary artery disease. The seeds of information about reducing the buildup of fatty substances that clog the heart's arteries and lead to heart attacks were planted many decades ago. Pioneers in the field have long preached against such evils as smoking, for such virtues as exercise and a lean diet. Dr. Paul Dudley White, who founded cardiology at the MGH in 1914, was perhaps the foremost of these leaders. Certainly Dr. White popularized these ideas with the American people. He preached by example as well as words. His bicycle rides became a symbol of fitness. When he ate in a restaurant, he would ask the waitress to substitute margarine for the pat of butter she served. (Until recently, of course, there was no significant evidence indicating that margarine too may have disadvantages for arteries.)

In 1979 Dr. Alexander Leaf, then MGH Chief of Medicine, started the MGH Cardiovascular Health Center. Its purpose was primarily to interrupt the backflow of patients who would be sent home from a Coronary Care Unit, only to return a year or two later with another heart attack. By teaching heart attack survivors to modify their life styles, the Center sought to keep them from returning to intensive care beds. Patients exercise — including running around an indoor track — are taught a healthy diet, are weaned from smoking, and learn how to take care of their bodies with emphasis on the muscle we call the heart.

A page 1 article in this issue announces a new advance. Building on the Cardiovascular Health Center, Dr. Valentin Fuster, Chief of the MGH Cardiac Unit, has appointed Dr. Richard C. Pasternak to create a coordinated network which will labor toward the goal of prevention of heart disease. Dr. Pasternak, who trained at the MGH in the 1970s, has identified a group of physician and nonphysician experts to join the effort. The article explores many of the areas into which these experts will delve: Among the aims are educating other health professionals, improving the health of women, research, seeking answers to many of cardiology's unanswered questions, and determining how best to apply the general knowledge which already exists to the specific needs of individual patients. The agenda is ambitious. The longterm results can be extraordinary. ■

## — Heart Disease

*(Continued from Page 1)*

***also internists, nurses, physical therapists, psychiatrists, research scientists, and many others.***

As the new MGH Director of Preventive Cardiology, he is bringing together just such a group under what he describes as the "umbrella" of heart disease prevention. "Our intention," he said, "is to start with the strengths of the people already working in the area and to build a much more flexible, integrated program."

The group's efforts will be targeted both at halting the progression of established heart disease and at preventing the development of cardiac problems in people with such risk factors as high blood pressure (hypertension), elevated blood cholesterol, and a family history of heart disease.

"When I first began talking with Valentin Fuster [Chief of the MGH Cardiac Unit] about coming to the MGH," Dr. Pasternak said, "he told me that he viewed prevention as one of the most important aspects of cardiology for the next decade. Having leaders in the field recognize prevention as a top priority — which is a real change in many circles — is going to make a difference for many, many people."

Although this will be the first time that all MGH heart disease prevention efforts have been coordinated, such programs are not new to the hospital. The MGH Cardiovascular Health Center was founded in 1979 under Alexander Leaf, MD – along with nurses Kris Nelson Tesar, RN, and Kathy McKool, RN, MS, and dietitian Carolyn Crimmins Hintlian,

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PHOTOGRAPHS: Pages 1, 3, 5, 7, 8 photographs, Susan McGreevey; Page 4 MR images, courtesy of Dr. Ralph Weissleder; Page 6 illustrations, MGH archives.

MS, RD — to help people recovering from heart disease and those at high risk improve their health through exercise, diet, and other lifestyle changes (*MGH News*, December 1979 and December 1985).

Until earlier this year, Dr. Pasternak (who trained at the MGH) was Director of the Coronary Care Unit and Codirector of Cardiovascular Training at Beth Israel Hospital. There he founded a Cardiovascular Health and Lipid Center and established a clinical trial group to conduct studies in diverse areas of preventive cardiology. Several of the group's researchers are joining Dr. Pasternak at the MGH to continue their investigations.

"Dr. Pasternak brings an expertise and talent that will help us develop innovative research and education ideas in cardiac disease prevention and rehabilitation," Dr. Fuster said. "And he will help us bring these programs to the patients who need them."

Describing the major change in thinking about heart disease prevention, Dr. Pasternak explained, "If you stood in front of an audience 15 years ago and said we could halt the progression of coronary disease in the arteries, no one would believe you. It was thought to be inevitable that once you had coronary artery disease it was going to progress. Now we know that the disease is much more dynamic than was ever believed."

That knowledge has come through the work of scientists like Dr. Fuster who have made major contributions to understanding the process of atherosclerosis. This condition is characterized by the development of plaques (deposits of fat and cholesterol) inside major arteries.

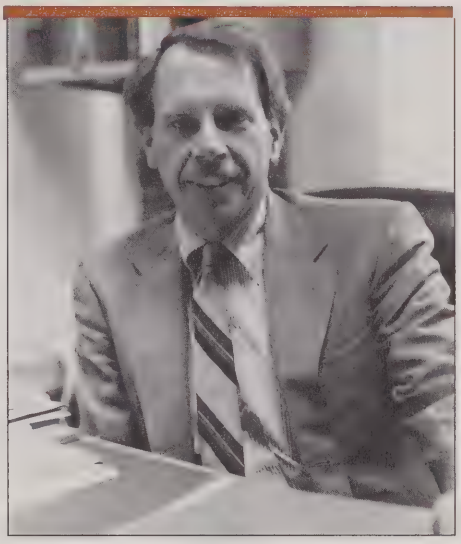
The new evidence that the buildup of plaques can be halted or even reversed comes from researchers at several institutions who have shown the effectiveness of such techniques as reducing blood levels of lipids (fats and cholesterol) through diet and medication, increased exercise, and stress reduction.

"There are a lot of pieces of data suggesting that, in some patients, coronary lesions can be made smaller," Dr. Pasternak said. "But exactly who those patients are and which interventions work best in which combinations, that has to be determined."

The broad base of the MGH prevention effort, the many groups and specialties it will bring together, should help better define each intervention's appropriate role. Addressing questions related to cholesterol will be members of the MGH Lipid Group, led by Mason Freeman, MD, along with Dr. Pasternak's clinical trial group.

"We need to better understand some of the new lipid-lowering drugs and test some of those that are not yet approved to learn more about how they work," said Dr. Pasternak. "And we want to investigate whether any unusual aspects of blood lipids might be new indicators of risk."

***The collaborative prevention network also will include an expansion of the outpatient Cardiovascular Health Center and the inpatient Cardiac Rehabilitation Program managed by Physical Therapy. Other activities directed at cardiac patients — in Nursing, Dietetics, Social Services — will be integrated into a comprehensive program that addresses patients' needs from their first admission through outpatient followup.***



*Richard C. Pasternak, MD*

In the area of primary prevention — preventing disease from ever developing — Dr. Pasternak plans efforts to target specific risk factors, number one of which is smoking. A new Quit Smoking program, based in the Cardiac Unit, will be led by Nancy A. Rigotti, MD, an internist with extensive clinical and research experience in smoking cessation.

Collaborations also will be established with people throughout the hospital addressing high blood pressure. Among participants will be the Cardiovascular Research Center in Charlestown, directed by Mark Fishman, MD.

***Dr. Pasternak explained, "We hope to bring together both people working in the basic sciences and those in the clinical realm of hypertension. An important goal is making information that scientists learn more readily available to those providing patient care."***

The role of stress in promoting cardiovascular disease has become more clear in recent years, but studying it presents some challenges. While cholesterol levels, blood pressure, even the number of cigarettes smoked in a day can be measured, there is no simple way to quantify an individual's stress.

"Researchers have been struggling for several decades to come up with objective measures of stress," Dr. Pasternak said. "We hope to consolidate that work and develop concepts that will be more useful than such popularized notions as 'type A personality'."

A group of psychologists and psychiatrists — led by Andrew Littman, MD — will develop behavioral intervention strategies to alleviate stress and support activities in both the smoking and cardiac rehabilitation programs.

***As the prevention programs grow, Dr. Pasternak anticipates adding a significant educational component. "One of the problems in the cardiology community has been a deficiency in teaching about preventive services," he said.***

"There also needs to be more communication between cardiologists and those working in public health and epidemiology. We hope to develop a productive interaction to work on some of the new National Institutes of Health initiatives, which could take real advantage of the strengths we have at the MGH."

With the establishment of solid collaborative programs in patient care and in clinical research, Dr. Pasternak expects to build a variety of educational efforts. These could range from medical student clerkships, to clinical and research fellowships, to continuing education courses.

Another area he is very interested in is women's health issues. He directed the formation of an MGH group that, working with colleagues at the Beth Israel, will investigate how certain interventions might improve both cardiovascular health and overall health in women. The group hopes to receive funding from the Women's Health Initiative of the National Institutes of Health.

Dr. Pasternak's long-term vision for the preventive cardiology program rests firmly in the broad base of services and expertise found at the MGH.

***"One can't really take a single approach to this problem. Each patient is a different person with a unique set of needs and risk factors. We plan to provide a range of resources for the primary care physician or the cardiologist who is addressing a particularly tricky clinical problem. At the same time we hope to learn from our experiences and to foster ways to share this knowledge with our colleagues across the country."*** ■

# — MRI — Images of the Future

*(Continued from Page 1)*
contrast agent through the heart's blood vessels, revealing exactly how much blood is delivered to an area of the heart at a given time.

***However, a unique agent developed by Dr. Weissleder is revealing important information about the damage done when a heart attack (myocardial infarction) cuts off the blood supply to a part of the heart.***

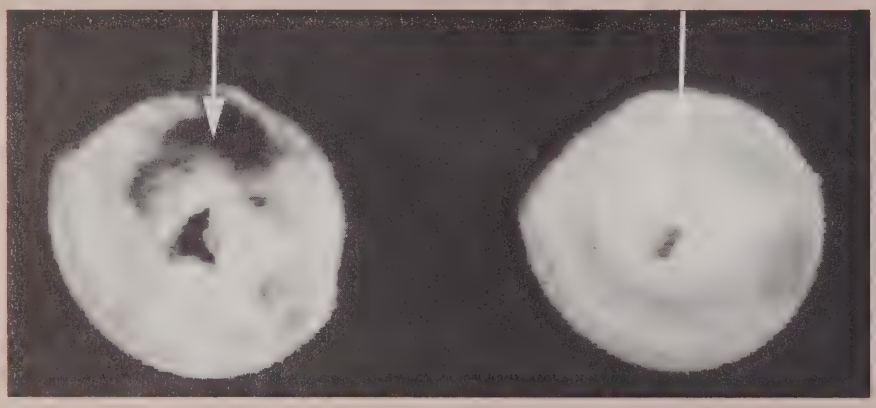
The compound is the first to add a magnetic label to a monoclonal antibody (MAb). These are genetically engineered versions of immune system components that recognize and bind to a specific protein — in this case myosin, a muscle protein prominent in heart muscle.

When injected into the bloodstream, the myosin MAb travels and binds to heart muscle that has been damaged in an heart attack. The magnetic label shows exactly which portion of the heart has lost its blood supply. Dr. Weissleder and his colleagues are currently conducting animal studies of the agent's use.

Another strategy is being investigated by Van Wedeen, MD, who in the early 1980s played a major role in developing MR angiography (imaging of blood vessels) at the MGH. Now he is working on techniques to measure the motion of the heart muscle.

Bruce Rosen, MD, PhD, MGH Director of Clinical NMR, explains, ***"Van is developing ways to measure, in great detail, how well any given part of the heart is able to contract. That ultimately determines how well a patient will recover from a heart attack."***

Dr. Rosen adds that this totally noninvasive technique could help answer the critical question of whether a section of heart muscle damaged in a heart attack was completely dead or whether it was "hibernating" and could be revived if the blood supply was renewed by bypass surgery.



***These MR images show the hearts of animals whose cardiac muscles have the kind of damage caused by a heart attack. The arrows indicate the areas of damage. In the image on the left, the animal was injected with a new MR contrast agent that includes a special component attracted to the damaged muscle. The image clearly shows the affected area. Standard contrast agents, used in the image on the right, cannot show such muscle damage.***

Dr. Brady noted that cardiac MR imaging would not completely replace existing techniques such as cardiac catheterization, which have their own specific advantages. However, cardiac MR may be capable of diagnosing coronary problems that other techniques cannot now find.

"As MR becomes both faster and more sensitive to things like ischemia [lack of blood supply] and coronary artery disease, we may be able to provide integrated cardiac exams that look at structure, function, and blood supply in a single examination. This would be much more cost effective than the several procedures currently required to provide this information," he said.

***A different sort of contrast agent developed at the MGH has potential for both diagnosing and possibly treating cancers that have spread to the lymph nodes.*** These nodes are part of a system carrying lymphatic fluid — a clear liquid containing various immune system components — throughout the body.

Cancer cells originating in other parts of the body often are transported to the lymph nodes, which act as filters for the lymphatic system. There the tumor cells may grow into secondary cancers, called metastases.

Detection of lymphatic metastases is difficult because it is impossible to visualize most nodes with standard imaging techniques. Contrast agents are used in some nuclear medicine and CT scan examinations; an injected agent shows up in nodes near the site of the injection. However, this technique cannot image the majority of nodes, which are located deep in the body.

What was needed was an agent that would selectively locate in lymph nodes throughout the body. To develop such an agent, Mikhail I. Papisov, PhD, a research fellow working with Drs. Brady and Weissleder, searched for any substance that was naturally attracted to lymph nodes.

"Researchers in this lab found one compound that, to a small degree, concentrated in the lymph nodes after intravenous injection," Dr. Papisov said. "Then we discovered the special structure on the surface of that compound that was responsible for this concentration and were able to improve that structure's attraction to the lymph nodes."

With this knowledge, Dr. Papisov and his colleagues constructed a large molecule coated with these structures. Inside this polymer (a molecule made up of several smaller parts), they placed an MRI-detectable contrast agent. In animal studies, the compound has proven very effective for visualizing lymph nodes.

Dr. Papisov explained that further animal tests are required to check for toxic effects before the compound can be tested in humans. Although there could be some risk from a substance that interacts with the immune system, so far there are no signs of problems.

If this compound proves safe, it promises significant advantages in patient care. The way it collects — or doesn't collect — in the lymph nodes could signal the presence of small metastases and the degree to which cancer has invaded the nodes.

***Even more significantly, the compound could theoretically be used to transport anticancer drugs directly to cancerous lymph nodes.*** The drug would be encased in the interior of the polymer molecule,

*Keith R. Thulborn, MD, PhD, makes adjustments to a copper coil that will produce the magnetic field in an MRI machine.*

protected from the body's immune system, and would be unable to affect tissues in other parts of the body.

Dr. Weissleder is also working on MR contrast agents that are combined with anticancer, antibiotic, or blood-clot-dissolving drugs. These compounds might be particularly useful as an adjunct to minimally invasive surgery, operations performed through tiny openings using fiberoptics, lasers, and other advanced techniques.

For example, a contrast-labeled anticancer drug could be introduced into an area from which a tumor has been removed. The MR label allows physicians to monitor whether the drug stays in the desired location and how much of it remains over time. Similarly a labelled clot-dissolving drug, delivered to the site of a heart attack through a tube (catheter), could be tracked with MRI.

In one of the newest MRI applications being explored at the MGH, Keith R. Thulborn, MD, PhD, and colleagues are producing images with atoms other than hydrogen (used for standard MR imaging), primarily sodium and phosphorus. The images they obtain reflect not the structure of an area but its metabolism, the physiologic and chemical activity of the tissues.

It can show how active cells are, whether they are growing or dying, and the quantities of biological chemicals present in tissues. ***The technique could provide a highly accurate assessment of cancer treatment, showing not just the size of a tumor but also how much of its volume consists of living cancer cells.***

Dr. Thulborn explained that this kind of information used to be gathered by a related technique called NMR spectroscopy, which has been used for decades to analyze the chemical structure of molecules. However, earlier methods produced inexact information.

The strength of the NMR signal could be affected by the equipment used to measure it, in addition to the composition of the sample itself. It also was not possible to differentiate between the signal produced by a lot of inactive cells and that of a few very active cells.

"Our technique gives us an unambiguous, quantitative [numerical] reading that does not depend on the instrument's response," Dr. Thulborn said. "By measuring the cell density within a tumor, we should be able to gauge the response to treatment. Current techniques that look only at tumor volume are fairly insensitive to the changes produced by therapy."

Sometimes an area of investigation leads to an unexpected patient-care application. A group led by Leo Garrido, PhD, had been using MRI to explore the physical and chemical properties of plastics and other non-living solids. Their study into silicone compounds was originally targeted to industrial uses. But it gained new importance when concern developed over silicone breast implants.

Now they are investigating how silicone changes after implantation in animal and human models and are looking for ways to locate concentrations of silicone in the body.

Probably the single most powerful constraint on future applications of MRI is cost. "If it weren't for the financial crisis in health care," Dr. Brady noted, "I'd say that, within the next ten years, most diagnostic procedures could be done by MR. As it is, cost issues will understandably temper how the technology proliferates."

Even so, MRI's potential is very powerful. James H. Thrall, MD, chief of the MGH Department of Radiology, sees it as combining the strengths of other available imaging techniques.

"MRI brings together the structural imaging ability of computed tomography [CT scan] and conventional x-rays with the functional imaging capabilities found in nuclear medicine and angiography. As such, it is the single most versatile imaging modality we have." ■

# REMEMBERING THE COCOANUT GROVE

No one who lived in Boston at the time will forget November 28, 1942: the date of the Cocoanut Grove fire. Nearly 500 people died that night when fire swept through the popular Boston nightspot.

Panicked crowds were trapped behind doors that were locked or blocked by others stampeding from the inferno. Although many were burned, more were felled by dangerous gases released by burning materials.

Although nothing can diminish the scope of the tragedy — certainly one of the worst in modern civilian history — a few fortunate circumstances made the difference for some who ultimately survived the blaze.

While most of the initial survivors were sent to Boston City Hospital, then the city's designated institution for accident victims, the second largest number were brought to the MGH. Probably no institution in the country was better prepared for coping with such a disaster.

In the months since the bombing of Pearl Harbor, just under a year before, the hospital had developed a disaster plan. Anticipating the possible need to deal with large numbers of patients from the war, Drs. Nathaniel W. Faxon, MGH General Director, and Edward D. Churchill, Chief of Surgery, devised a program specifying emergency duties for hospital personnel. The administration could quickly find out which floors could be readily evacuated for incoming patients.

***But even more important was the research done by Dr. Oliver Cope, MGH endocrinologist and surgeon, in burn treatment. He was challenging the accepted methods, which involved removing blisters, cleaning the wound, and spraying it with tannic acid (used to tan animal skins).***

Although the process did create a protective cover over the burn, it was painful and extremely time consuming, requiring four or five people to care for each patient. Dr. Cope believed that by leaving blisters alone and covering the area with petroleum jelly and sterile bandages, the burn would heal. While burn patients would still require very intensive care, far fewer people would be required to maintain the dressings, a significant advantage if many patients had to be cared for.

Dr. Cope also believed that not enough attention was paid to restoring the fluids lost through burned skin. While doctors and nurses worked to maintain the tannic acid covering, patients were dying of dehydration.

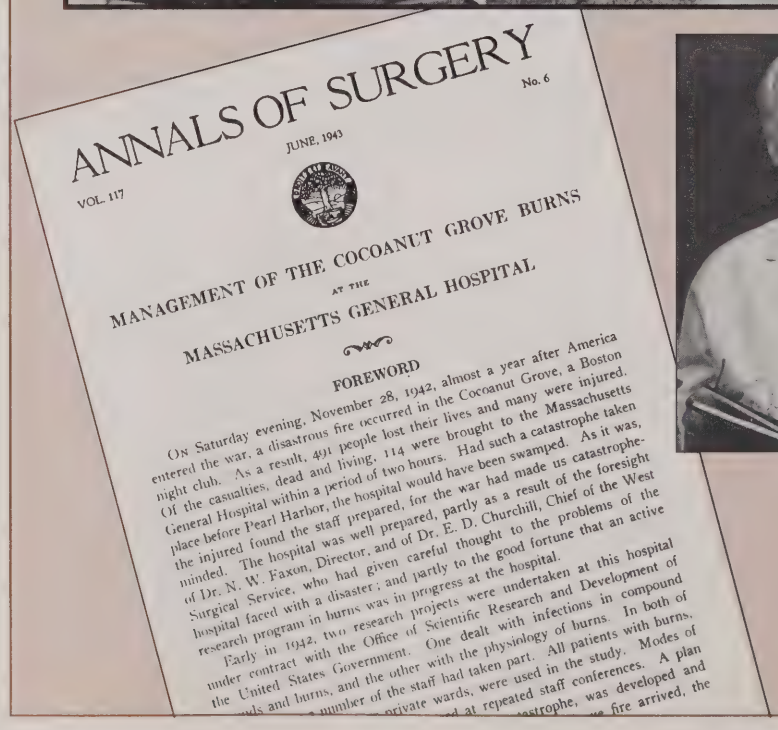
As part of a National Research Council review of emergency practices, set up in the wake of the Pearl Harbor bombing, Dr. Cope presented his ideas to a government committee. He returned to the MGH 10 months before the Cocoanut Grove fire with a grant to test his concepts. The technique was used on 73 patients before the nightclub disaster.

In addition, Dr. Cope put together a formula for anticipating the fluid needs of burned patients and for preventing shock – the dangerous drop in blood pressure that occurs whenever the body undergoes a trauma. His group also showed the importance of caution in using antibacterial sulfa drugs – penicillin was not generally available – to prevent the development of kidney complications.

Of 114 people brought to the MGH from the fire scene, all but 39 either died before they arrived or within the first two hours. The surviving patients were taken to the sixth floor of the White Building, which had been quickly evacuated under the hospital's disaster plan.

Dr. Cope's method for treating burns was not only effective, it also freed the hospital staff to deal with an unexpected complication — serious respiratory damage.

All but three of the MGH patients had lung damage caused by inhaling hot, toxic gases released in the fire. Fluid leaked from damaged areas of the lung, just as it did from a surface burn, putting patients in danger of drowning in their own fluids.



ANNALS OF SURGERY

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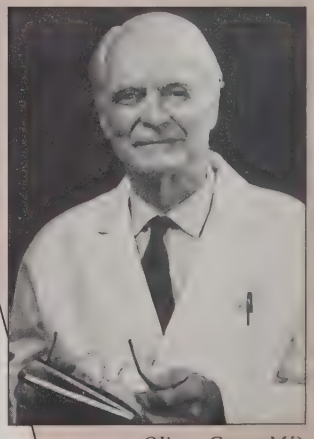
MANAGEMENT OF THE COCOANUT GROVE BURNS AT THE MASSACHUSETTS GENERAL HOSPITAL

FOREWORD

On Saturday evening, November 28, 1942, almost a year after America entered the war, a disastrous fire occurred in the Cocoanut Grove, a Boston night club. As a result, 491 people lost their lives and many were injured. Of the casualties, dead and living, 114 were brought to the Massachusetts General Hospital within a period of two hours. Had such a catastrophe taken place before Pearl Harbor, the hospital would have been swamped. As it was, the injured found the staff prepared, for the war had made us catastrophe-minded. The hospital was well prepared, partly as a result of the foresight of Dr. N. W. Faxon, Director, and of Dr. E. D. Churchill, Chief of the West Surgical Service, who had given careful thought to the problems of the hospital faced with a disaster; and partly to the good fortune that an active research program in burns was in progress at the hospital.

Early in 1942, two research projects were undertaken at this hospital under contract with the Office of Scientific Research and Development of the United States Government. One dealt with infections in compound ...uds and burns, and the other with the physiology of burns. In both of ... number of the staff had taken part. All patients with burns, ... private wards, were used in the study. Modes of ... at repeated staff conferences. A plan ...astrophe, was developed and ... fire arrived, the



*Oliver Cope, MD*

With the new Blood Bank established just seven months before, the MGH was well-equipped to handle huge quantities of blood and plasma. Even so, the needs of Cocoanut Grove patients were so acute that orderlies were sent out to nearby Charles Street the night of the disaster to ask passersby for donations. Many complied, and the Blood Bank accommodated a steady stream of donors until noon the next day.

To care for patients on the White 6 ward, special sterile procedures were set up, reducing the danger of infections. All equipment was sterilized, and doctors and nurses wore masks and gowns as though entering an operating room.

At the time of the fire, Alma Cady Robbins, RN, was an instructor in nursing practice in the MGH outpatient area. She was one of many off-duty staff called in to assist the morning after the tragedy. She recently recalled that, during the subsequent weeks, many hospital staffers regularly worked double shifts to care for the burned patients.

"After our usual day shift, we would go up to the wards to help out with general nursing services," she said. "The patients needed a very intense level of care, but even in the evenings we always had adequate staff because all of us were working extra time as volunteers. I wondered where we got the stamina."

The emotional impact the disaster had on the patients — many of whom had friends and relatives who had perished — was not always apparent to the doctors and nurses struggling to keep them alive. But the Social Service staff was alert to such problems. Psychiatrists Dr. Eric Lindeman and Dr. Stanley Cobb were brought in to help patients cope with the trauma they had experienced.

***Only a month after the fire, the National Research Council recommended adoption of the MGH burn therapy techniques throughout the government and armed forces. The knowledge gained in treating Cocoanut Grove survivors — both at the MGH and at Boston City — saved countless lives during World War II.***

Out of the 39 MGH patients, seven died of respiratory injury, none from burns. Among the survivors was Martin Sheridan, a freelance writer who went on to work as a war correspondent for the *Boston Globe*.

Mr. Sheridan, now living in Connecticut, recently recalled his experience. "The care at the MGH was excellent because of the program they'd developed for the government for treatment of burns. I was very fortunate to have been taken to the MGH from the very beginning." ■

# Book Helps Parents Decipher *Kid's Symptoms*

WHAT DOES IT MEAN when a child has a cough, a rash, a fever? What can parents do to treat common health problems? When should parents call the doctor; when should they rush to the emergency room?

Everyone with children has wrestled with such questions. And in an effort to help parents find their way through an often confusing maze of medical advice and information, MGH pediatrician Ralph E. Minear, MD, has written *Kid's Symptoms*, recently published by Avon Books.

"When I talk with parents, they always have lots of questions about what they can do to help with their child's care," explained Dr. Minear, who is Chief of Pediatrics at the MGH's Bunker Hill

*(Concluded on Page 8)*

## Excerpt from *Kid's Symptoms*

*(From the section on fever)*

### *Urgency Alert*

*Ordinary Concern:* With a child one year old or older, who has no other complaints or symptoms, parents may conduct home monitoring of a temperature of 101° F, which lasts for eight hours of less.

*Yellow Alert:* The doctor should be called within a reasonable time period when:

- the child's temperature is greater than 101° F for more than 24 hours, and there are no other complaints
- the temperature of the child is 101° F or lower for 72 hours, but then it rises above 101° F or goes up and down to 101° F during a period of three or more days
- the child is older than two years of age and his behavior is abnormal.

***Red Alert:*** The doctor should be called immediately when:

- the temperature is 105° F or greater in a child of any age
- a baby under six months of age has a temperature of 101° F or more
- a baby younger than three months has any fever at all
- symptoms such as deep coughing are present and have been previously linked to a serious condition, such as pneumonia
- convulsion occurs with a fever
- the child's temperature is 101° F or higher and the child's physician has previously diagnosed a special condition of the heart, lungs, kidneys, nervous system, or blood.

### *Parent's Response*

Before you can accurately evaluate your child's fever, you must do more than just place your hand on his forehead. It's essential to use a thermometer — either one of the traditional glass mercury types or the digital kind.

The best thermometers are glass with mercury. The ones with a long, thin bulb are designed for oral use. The ones with a short, fat, round bulb are for rectal use. Either of these types may be used under the arm. Electronic digital thermometers are good but expensive. Forehead straps aren't reliable and are not recommended. Those designed as a pacifier are also unreliable and not recommended. Disposable oral dot thermometers are not reliable and not recommended.

*Ralph E. Minear, MD, gives a checkup to year-old Allan Parrelli.*

## — Kid's Symptoms

*(Concluded from Page 7)*

Health Center in Charlestown.

"As a pediatrician, I thought I'd look into the information that was available to parents in books and other resources. And I tried to approach it from my own experience as a parent, in terms of starting from the symptoms anyone would understand — like a cough, fever, or stomach ache — instead of from the perspective of specific diseases."

Dr. Minear felt that most of the available materials on children's health were too technical and decided to produce his own book. In organizing the material, he kept in mind the kind of exchange that usually occurs between parents and the pediatrician.

"They tell me the child's symptoms; I ask them questions to narrow down possible diagnoses. It's really a partnership between the physician and the parents," he said.

The book's sections are brief and are built around such common symptoms as headache, constipation, fainting, or runny nose. Also addressed are more serious conditions including burns, seizures, and diabetes.

Dr. Minear reviews possible causes for the symptoms and describes signals that may point to the specific cause.

For possibly serious symptoms there is an "Urgency Alert," which outlines when there is little cause for concern and when a doctor should be consulted, either soon or right away. Situations indicating a possible emergency are highlighted, with instructions to take the child to a local hospital immediately.

Also included are more detailed descriptions of the actions parents should take to help the child and evaluate the symptoms. Over-the-counter medicines to use or to avoid are described, as are general tips that can help avoid worsening of symptoms.

"One of the things that can be most confusing for parents is differentiating between colds and allergies or asthma," he explained.

"I try to help them understand the variety of reasons a child could have a cough and describe some of the things a physician uses in forming a diagnosis. If they know the child may have asthma, that could change the decisions they make about bringing the child in."

Dr. Minear describes what parents can expect when taking their child to the doctor or emergency room — the kinds of tests that may be ordered and the questions that may be asked.

"It's helpful to let parents know what the physician is going to do when they bring their child to the hospital. Parents can get very anxious and confused in that situation," he said.

"If they know what's going to happen, they feel more reassured. The more informed they are, the better they can participate in their child's care."

Dr. Minear hopes the information in *Kid's Symptoms* will help parents cut through the often bewildering array of information encountered in the media, including medication advertisements. He noted that parents today rarely live in the communities in which they grew up and may not have access to support and information provided by family members from older generations.

As stressed throughout the book, Dr. Minear said that, in potentially urgent situations, parents should not worry about "bothering" their doctor or about bypassing the doctor and going right to the emergency room.

"If your child doesn't look well and you're afraid you can't handle it, you need to call the doctor or the emergency room; follow your instincts. I'd never be offended if parents who couldn't reach me took the child straight to the hospital. It's the right thing to do." ■

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MGH News

Vol. 51 No. 8 December 1992

*Dolores Dunne positions a patient for a mammogram in the MGH Breast Imaging Center.*

# New Center Takes Multispecialty Approach to Breast Cancer

WOMEN diagnosed with breast cancer today are faced with more choices than ever.

They can not only choose among several surgical procedures to remove a tumor but also may need to consider supplementary treatment with anticancer drugs or radiation therapy. Women who undergo a mastectomy (surgical removal of a breast) have several options for reconstruction.

These choices bring the involvement of many physicians and health care professionals. To coordinate all efforts directed toward detecting, treating, and someday preventing breast cancer, the MGH has established a Comprehensive Breast Health Center. Barbara L. Smith, MD, PhD, has been named the center's director.

"One of the crucial elements in establishing this effort was finding the ideal person to direct the center," said Kurt J. Isselbacher, MD, director of the MGH Cancer Center.

"Dr. Smith is an outstanding physician/scientist who has been actively involved in breast cancer research. In addition to being a superb surgeon she is what, to us, was equally important: a kind, caring, and compassionate physician."

"Dr. Smith comes with an extensive background and experience in the care of patients with breast disease. We are very fortunate to have been able to attract her to the MGH," said W. Gerald Austen, MD, Chief of General Surgical Services.

Dr. Smith explained that the new center will have three primary goals: to offer routine breast examination and screening services, to provide consultation and treatment for women with breast lumps or diagnosed breast cancer, and to compile information that will be useful to researchers.

Staffed by a team of specialists in every aspect of breast care, the center will be a resource to the MGH staff and the wider medical community. Its underlying philosophy is to allow each individual woman to take the most active role she may choose in the decision-making process.

***"Today we work with the woman in a partnership," Dr. Smith said. "It's less that we present a care plan to her and more that she works with us to create it."***

This increased participation, improve-

*(Continued on Page 4)*

# Intensive Care Services Help Give Kathleen a New Start

UNTIL their daughter Kathleen was born this past June, Janice and Joe MacMunn of Hudson, Mass., had no idea that anything was wrong. But the delivery room team at Framingham Union Hospital, knew right away that the baby was in trouble — she was having difficulty breathing, and her skin color, an important indication of a newborn's heart and lung function, had a bluish tinge.

Within a few hours the MacMunn's pediatrician told them the bad news. Kathleen had Down syndrome, a condition characterized by mental retardation and accompanying physical problems. In her case, one of these problems was with her heart.

In order to provide the level of care Kathleen needed, as well as to determine exactly her heart defect, a special MGH transport team brought her to Boston for admission to the hospital's Neonatal Intensive Care Unit (NICU).

As with all babies admitted to the NICU, Kathleen was transported by an MGH team consisting of a specially trained nurse and physician. Throughout the trip, the team carefully monitored her heart rate, oxygen level, breathing, and temperature — providing a level of care comparable to what she would receive in the NICU itself.

Caring for critically ill newborns like Kathleen requires the right combination of high technology and compassionate nurturing. For more than 20 years the MGH has been a regional leader in intensive care services for infants in its NICU, and for young children in its Pediatric Intensive Care Unit (PICU). Many of the infants admitted to the

*(Continued on Page 2)*

INSIDE

**Kids in the Hospital**
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**Recreating the First Cells**
*Page 7*

EDITORIAL

# New Breast Health Center; Superb Chief

BREAST CANCER CARE at the MGH has never looked better. The opening of the Comprehensive Breast Health Center is the first and foremost reason. With the various elements of excellent breast cancer specialties long in place, the MGH has for years been in a position to offer women very good care. The recent appointment of Barbara L. Smith, MD, PhD, as director of the new center brings all these elements together to raise the level of care even higher. A page 1 article in this issue describes the center and Dr. Smith, who blends the qualities of compassion, dedication, superb education, experience, and leadership. In the spring the new center will have centralized quarters to make it more convenient for patients and professionals.

Stephen H. Friend, MD, PhD, will give that center a unique dimension. He has begun collecting blood samples from 400 women who had breast cancer before they were 40. In a few years he hopes to be able to examine blood samples sent from women in Taunton, Toronto, or Tibet and tell whether they carry a gene that increases their risk of developing breast cancer. One drug is already being tested as a possible way to reduce those chances.

A third element is in place. Led by Albert G. Mulley, MD, Chief, General Internal Medicine, a team has created two videodisks for women with breast cancer. Dr. Mulley's group developed the videodisks as a significantly improved means of providing women diagnosed as having breast cancer with as much information as they need and want. Part of a series of videodisks on a variety of diseases, the interactive television disks give each woman control of how much information she receives. New patients of the MGH Comprehensive Breast Health Center are already using the interactive disks. Several whose breast cancer had been diagnosed and treated before the arrival of the system have also seen it. Their common reaction: "I wish this had been available when I learned about my condition." ■

# Life's Oldest Mystery

A PAGE 7 ARTICLE is about the oldest mystery of life on planet Earth. What were the first cells made of? What did they look like? One might ask why hospital molecular biologists care. Like Sir Edmund Hillary who climbed Mt. Everest because it was there, Dr. Jack Szostak and his laboratory are fascinated because the mystery is there. Scientists can but guess at the answer. As with all basic research, however, the scientists who pursue it have no idea where the project will end. What seems remote, in this case a riddle millions of years old, could lead in unexpected directions that may one day have very practical implications for health in the twentieth and twenty-first centuries. That is the magic of basic research. Its serendipitous findings often lead to a barrel full of practical benefits. ■

## — Kathleen

*(Continued from Page 1)*

MGH NICU have problems with their heart and lungs as Kathleen did. Her breathing difficulties resulted from her heart defect.

Peter Lang, MD, Chief of Pediatric Cardiology, used two sophisticated techniques to diagnose the problem: echocardiography, which defines the heart's structure with sound waves, and cardiac catheterization, in which motion pictures of the heart and its blood vessels are taken via a tube called a catheter, threaded through a vein.

Kathleen had a complete atrioventricular canal (CAVC) defect. It is a common heart problem among babies with Down syndrome, although other children may also be born with the condition.

Normally the heart has four chambers, an upper and lower chamber on the right side and a similar pair on the left. On both sides, the upper and lower chambers are separated by a valve that helps control the flow of blood. The right side, which carries oxygen-depleted blood, and the left side, which carries oxygen-rich blood from the lungs, are separated by a wall of tissue.

In CAVC, there is no separation between the right and left sides of the upper and lower chambers. And instead of two valves, there is only one. Essentially, the heart of a baby with CAVC is comprised of two large chambers in which oxygen-rich and oxygen-poor blood mix.

This causes several problems. Because the heart's pumping action is inefficient, it is unable to move enough blood with each beat — a condition called conges-

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tive heart failure. Blood and other fluids can pool in the lungs, making breathing difficult. In addition, the blood that is carried throughout the body is not as rich in oxygen as it should be.

CAVC is treated with open-heart surgery. Without the operation, permanent lung damage could occur, limiting the child's overall growth. Physical exercise would be difficult, and there would be a constant risk of pneumonia or other life-threatening complications.

The skilled care provided in the NICU stablized Kathleen's condition soon after she was admitted. Her parents arrived at the MGH the next day, after her mother was released from Framingham Union.

They were understandably overwhelmed by the situation they were facing. "At first we didn't realize how serious her heart problem was," Janice said. "We were still in shock."

David Todres, MD, director of the NICU and PICU, explained that their reaction was typical. "Parents go through nine months expecting a perfect baby, and then there's a serious problem," he said. Instead of bringing their baby home, they come to this high-technology environment, where the lights are always on, where it's busy all the time. It's terribly disorienting."

In keeping with the MGH philosophy that treating a child means treating the whole family, the NICU staff involves parents in the baby's care to the greatest possible extent.

"We want to make sure that parents know everything that's going on and are part of the decision-making process whenever they can be," said Cheryl Dowd, RN, NICU permanent charge nurse. "There are no restrictions on the visiting hours, and we encourage parents to touch the baby, talk to the baby, to really get to know the baby."

Kathleen's parents were surprised and pleased that they were able to hold her and feed her during her stay in the NICU. Her father Joe was particularly heartened that Kathleen's Down syndrome was not regarded as a tragedy by the MGH staff.

"The Down syndrome was the hardest thing for me to take," he admitted. "I expected people would be staring at us, making a big deal out of it. But nobody dwelled on it. ***One of the nurses told me she had a brother with Down's, and that he was a great kid. I was impressed by the way they handled everything."***

One thing the staff did do was put the MacMunns in touch with MGH social worker Susan Lockett, LICSW. She arranged for Kathleen to enroll in an early intervention program near her home.

These provide a full range of educational therapies and physical activities — including training for parents — starting in the first months of life. Such services can help children with Down syndrome and other developmental disabilities achieve their fullest potential as happy, often productive members of society.

Kathleen spent six days in the NICU, during which the staff made sure she was able to eat and gain weight. Medication was prescribed to strengthen her heart and prevent heart failure.

"We like to get the babies stablized and home with their parents as soon as possible," said Marsha Elixson, RNc, MS, pediatric cardiology clinical nurse specialist. "We put them on a high-calorie feeding formula to help them grow and try to schedule the surgery at about six months, earlier if possible, to avoid any lung damage."

Kathleen did well after leaving the hospital and was ready for surgery at four and a half months. She returned to the MGH for the repair, which was done by cardiac surgeon Gus Vlahakes, MD.

*Janice and Joe MacMunn at home with five-month-old Kathleen*

"Dr. Vlahakes had to be very creative," said Ms. Elixson. "He used a patch to separate the upper and lower chambers into right and left sides and reconstructed the single valve into two valves. This is the usual procedure for repairing this defect, but it takes a lot of surgical talent to construct two valves that will function properly."

A major reason this kind of delicate, open-heart surgery can be done on such young children is the intensive postoperative care delivered in the PICU.

Before the MGH's Ellison Building was opened two years ago, infants and children having heart surgery had to be cared for in adult ICUs. It was too dangerous to move them all the way from the operating rooms in the Gray Building back to the pediatric units in the old Burnham Building.

When the Ellison opened, the NICU and PICU were relocated to the new building's third floor, with a direct connection to the operating suites. Now children can receive post-cardiac surgery care in an environment designed just for them.

"A major recent development in caring for critically ill children has been improved understanding of their specific medical needs," said Luise Sethmann, RN, PICU permanent charge nurse. "There was a time when hospitals treated them as little adults, but through research we now have information that helps us tailor medication and other measures to each individual child."

The operation to repair Kathleen's heart took several hours — "The longest day of my life," said her father Joe. Despite his anxieties, the results were excellent. She was cared for in the PICU for four days before being moved to a regular pediatric floor. Twelve days after her surgery, she was back home with her parents.

"We can already tell that she is stronger," said her mother Janice, a week after bringing Kathleen home. "Her stamina and her appetite are much better. We're looking forward to starting the early intervention program with her. She's really a great kid."

Ms. Elixson added that the outlook for Kathleen is excellent. "She should be a healthy, active child — able to go to school, to play with her friends, to ride a tricycle."

Both of Kathleen's parents agreed that the support they received from staff members in both the NICU and PICU — as well as from Dr. Lang, Dr. Vlahakes, Ms. Elixson, and many others — made a real difference for them.

"We had tons of questions, and they answered every one," said Janice. "I'd call at 3 a.m. to see how she was doing, and everyone was very reassuring."

***"Maintaining good communication with the parents is like doing a delicate medical procedure," said Dr. Todres. "In both cases if you rush it, you will bungle things. We emphasize taking time to really communicate with the parents. It's just as important as any technical procedure, and the our staff does it superbly."*** ■

# — New Center's Approach to Breast Cancer

*(Continued from Page 1)*

ments in tumor detection and treatment, and the trend to shorter hospital stays for those who have surgery has changed the experiences of most women with breast cancer.

"There's less time when they are away from home, when they're not in control of their lives," Dr. Smith said. "We now can be much more optimistic when starting someone along this path. We can tell many women, 'You have an 80 to 90 percent chance of never having to deal with this cancer again'."

When it moves into its new quarters in the spring, the center will give patients the ability to consult with a whole team of specialists in a single visit. Until then, the staff is working to offer services in the most coordinated, integrated way possible.

Some of the MGH staff members who will take major roles in the center are Daniel B. Kopans, MD, in Radiology; Fritz Koerner, MD, in Pathology; Irene Kuter, MD, PhD, in Medical Oncology; and Simon Powell, MD, PhD, in Radiation Oncology.

***Among the newest resources to be offered through the center are two interactive videodisk programs to help women with early-stage breast cancer review their treatment options. The programs unfold like a television documentary but are tailored to meet the specific needs of each viewer.***

A computer analyzes such information as the woman's age, the size of her tumor, and whether the cancer has spread to her lymph nodes. Then it constructs a presentation that applies to her individual situation.

Medical information about breast cancer is interspersed with interviews of women who have survived the disease. After the basic presentation, the viewer has the option to learn more about such topics as what to expect in the hospital, what a woman's breast may look like after mastectomy or lumpectomy (removal of the tumor only), and how women's sex lives have been affected by the surgery.

The breast cancer videodisks were developed by Albert Mulley, MD, Chief of the General Internal Medicine Unit and colleagues at the MGH and Dartmouth Medical School. They are the newest of several educational programs — addressing such areas as back pain, prostate enlargement, and high blood pressure — available to MGH patients (*MGH News*, September 1991).

***"Today we work with the woman in a partnership. It's less that we present a care plan to her and more that she works with us to create it."*** ***— Barbara L. Smith, MD, PhD***

Dr. Smith comes to the MGH from the Brigham and Women's Hospital and Dana-Farber Cancer Institute. She received MD and PhD degrees from the Harvard Medical School/Mass. Institute of Technology Health Sciences and Technology Program.

As a graduate student, she investigated the early changes seen in cells as they become cancerous, using an artifical tissue-culture environment. Since then she has worked to apply those principles to studying the development of breast cancer, while at the same time concentrating on the disease in her surgical practice.

"Trying to find what happens when a

breast cell changes from normal to cancerous is an ideal project for someone with both a scientific and a clinical [patient-care] background," she said. "There are a lot of clinical clues that can help us form the questions to be answered by research."

Dr. Smith notes several significant questions in breast cancer research today. What causes the disease? Who is at highest risk? How best to identify the early stages? Which treatments are most effective for particular patients? Can the development of a tumor be prevented?

One tool that should be useful in addressing these questions will be a data bank of all patients treated in the MGH center. The center's staff will collect information on patients' medical backgrounds, risk factors, the types of tumors and size upon diagnosis, the treatments used, and their success or failure.

Scientists will be able to use this material, along with tissue samples for molecular studies, to relate the results of their investigations to actual patient histories and outcome.

"This isn't done in many centers," Dr. Smith said. "And it's really central to what we want to do here, to build a strong bridge between clinical practice and basic science with the overall goal of improving patient care."

One of the initial research efforts with which the center will be involved is a cutting-edge investigation into the role that inherited genetic abnormalities have in breast cancer. MGH molecular biologist Stephen H. Friend, MD, PhD, and colleagues are establishing a "library" of breast-cancer-associated genetic mutations that could eventually enable screening of high-risk women anywhere in the world. (See sidebar)

The MGH is also participating in the national tamoxifen study. This drug has been used for many years to treat women with breast cancer. Doctors noticed that women who took tamoxifen appeared to develop fewer new tumors in the opposite breast than normally would be expected.

The 10-year nationwide trial, sponsored by the National Cancer Institute, will enroll 16,000 women judged to be at high risk for developing breast cancer. Half of them will take the drug regularly, to see whether tamoxifen's apparent protective effect is real. Jerry Younger, MD, is coordinating the MGH component of that trial.

Improvements in mammography and related screening techniques are being pursued by Daniel B. Kopans, MD, MGH Director of Breast Imaging and his colleagues. Advanced technologies such as MRI (magnetic resonance imaging) and PET (positron emission tomography) could offer improved diagnostic power and accuracy over current practices.

MGH radiologists recently published a study supporting the safety and effectiveness of mammography for women under 50. Their results contradict controversial suggestions by a Canadian research group, which claimed that women age 40 to 49 were more likely to die from breast cancer if they received mammograms. The Canadian study has been criticized by many researchers for technical flaws.

Dr. Smith agrees that mammograms play an essential role in saving women's lives. "It is clear that in women over 50, mammograms are helping us detect cancers at an earlier, more curable stage. Although their benefit for younger women is not as clear, I think that women over 40 should have mammograms at least every other year. Many people would say every year."

Acknowledging that many women are concerned about the discomfort associated with the procedure, she added, "Yes it's true that a mammogram may hurt for a few minutes, but breast cancer hurts for years." ■

## *Pinpointing Genetic Causes of Breast Cancer*

IT HAS BEEN KNOWN for many years that cancer seems to run in certain families. And having a close relative with breast cancer significantly increases a woman's risk for developing the disease.

MGH scientists have played a major role in uncovering the genetic basis of several cancers. Now they are launching an effort designed to improve the detection of breast-cancer-associated genetic changes. Their initial goal is to compile a reference library of these mutations that could be used to determine the actual risk facing individual women.

The Breast Cancer Genetic Risk Evaluation Program is being led by MGH molecular geneticist Stephen H. Friend, MD, PhD. Dr. Friend published a 1990 study identifying mutations in a gene known as p53 that significantly increased the risk of developing breast cancer and several other malignancies.

"Although most people realize that one in eight American women will develop breast cancer, they may not be aware that the risk is not evenly distributed. Some individuals are at much higher risk, and we've been working to identify those people for the past several years," said Dr. Friend. At least three to five other breast cancer susceptibility genes are being sought, he added.

While the search for other cancer-associated genes continues at MGH and elsewhere, Dr. Friend and his colleagues will assemble their "library" by collecting blood samples from 400 women who were diagnosed with breast cancer early in life — at age 40 or younger. It is estimated that half of these women have a genetic defect predisposing them to the disease.

(Women of any age who developed breast cancer before age 41 and wish to participate in the project should call Deborah MacDonald, RN, MS, at 617 726-7803.)

As scientists discover new genes affecting a woman's risk of breast cancer, they can search the samples in the MGH library to find how often each gene is altered in women with breast cancer.

Dr. Friend's group is also working to improve the techniques used to find whether or not a woman carries a known genetic mutation. The process currently takes as long as a month, and the scientists hope to develop a test that answers the question within a day. The accomplishment would make it feasible to screen large numbers of women for genetic changes.

Barbara Smith, MD, PhD, director of the new MGH Comprehensive Breast Health Center, said the time is right to be able to offer such screening tests. ***"We wouldn't want to simply tell someone she was at increased risk for breast cancer if we couldn't do anything about it. But we are now on the edge of being able to give treatments that will reduce the risk of breast cancer ever getting started."*** ■

# Helping Kids Be Kids in the Hospital

WHEN CHILDREN enter the hospital, their world is turned upside down. Not only must they deal with the discomfort of an illness, injury, or operation, but the familiar faces and surroundings of their homes, neighborhoods, and schools are gone.

Staff members in the MGH Children's Service understand that special care is needed to help children — and their parents — deal with the stresses of hospitalization. Several programs address creating the most normal possible environment for them: one that will let kids be kids.

Denise Lozowski, RN, MSN, clinical nurse specialist for the MGH pediatric units, explained that young children are very focused on what is happening to them now, in contrast to adult patients who typically are as concerned with long-term effects that an illness may have on their careers or activities.

"It's very important to meet children's needs and address their concerns as they arise," she said.

One way that philosophy is put into practice at the MGH is giving children every opportunity to take part in activities they'd usually engage in at home or school. Each of the three pediatric floors has an elaborate recreation area with toys, games, and activities designed for that unit's age group.

"We try to provide the kids with an environment that's very normal, familiar, and comfortable, and with the opportunity to interact with other children on the unit," said Sally Cave, supervisor of the Child Life Department within the Children's Service.

Ms. Cave has worked with children at the MGH since the late 50s, when she was one of three "play ladies" in a pilot program sponsored by the Ladies Visiting Committee. Today she supervises a staff of professional child life specialists — as well as volunteers, college students, and graduate and medical students interested in child development.

She explains that even children who cannot get out of bed can be brought to the bright, spacious recreation rooms when they themselves choose. "We let them decide whether or not they want to participate. It's one of the few places where they can control what they do while they're in the hospital."

Several activities available to children — particularly drawing and painting — can help them express their feelings. Toy versions of medical equipment, surgical uniforms, and special anatomically complete dolls allow children to act out their experiences and anxieties and to understand better what is happening to them.

The Pediatric Preadmission Program offers a preview of a hospital visit to children with scheduled admissions and their parents. Lora Feltham, child life specialist, explained that children who have never been to a hospital before may create unrealistic fantasies about the experience. They may even think they're being punished for something they did.

During the preadmission visit children are introduced to the sights and sounds of the hospital through a puppet show for younger children or a videotape program for school age children. Medical toys, simple hospital equipment, and scrub uniforms are available for play and dressup.

"We discuss such things as why they will wear special pajamas, why doctors and nurses wear special clothes, and how they can tell when someone wearing a hospital mask is smiling," Ms. Feltham said.

Afterwards they tour the Same Day Surgical Area, and those who will be

***Left:*** *Young patients Jessica Acevedo (left) and Andrea Beloff (right) work on craft projects with Wheelock College student Marice Edouard in the Ellison 18 recreation area.*
***Right:*** *With the help of child life specialist Lora Feltham (left), Courtney Theriault "starts an intravenous line" in a special doll designed for medical play.*

admitted to the hospital visit the pediatric floors. Parents can pick up literature about the hospital's services and about materials providing further useful information.

"We hope this program will reduce the anxiety felt by both children and their parents," said Ms. Feltham. "We even encourage parents of infants and toddlers to participate, because small children can pick up on their parents' fears."

Involvement of parents in their child's care is a cornerstone of pediatric care at the MGH. Even before the spacious double-bedded rooms in the Ellison Building were opened two years ago, parents were encouraged to stay with their children (sometimes spending the night in a bedside armchair) and participate in their care.

This policy is a longstanding tradition. A 1974 article in *Boston* magazine said of the MGH: "[Parents] are regarded as essential to their children's care and are welcome round-the-clock. . . . It is surprising how well family centered pediatric care flourishes here."

"Illness affects everyone in a family, parents and siblings as well as the sick child," said Ms. Cave. "We really think in terms of caring for the whole family."

A support group at which adolescent patients can discuss their special concerns is being revived as well. And for those being treated for cancer, the School Reentry Program helps ease the transition back to daily life.

Started five years ago by Kathryn Pazola, RN, MSN, and Sheila Brown, RN, BSN, the program establishes contact between the child's primary nurse and the school to help ensure a smooth transition back to a normal school life. Nurses may visit the child's classroom and explain to the children what can be expected when their classmate returns. They also educate school nurses about childhood cancer and its treatment, as well as inform them about particular concerns related to the individual child.

"In the past, schools tended to isolate children who were recovering from cancer, perhaps having them ride the special needs school bus," said Julie McMahon, RN, Ellison 18 nurse manager. "That's particularly hard for adolescents, who want to fit in with their peers."

"Everyone here — nursing staff, medical staff, and therapists — is very committed to creating an environment that supports the child's point of view and priorities," stressed Ms. Lozowski. "That philosophy lies behind and goes beyond any programs we can offer." ■

# MGH Scientist Hopes to Recreate the First Cells

WHAT DID the earth's first living cells look like? Scientists may never have a definitive answer, but within the next few years they could get a good idea from the work of MGH molecular biologist Jack Szostak, PhD.

Dr. Szostak and his colleagues in the Department of Molecular Biology are trying to develop simple artificial cells that may be very much like the first living organisms to appear on this planet.

For many years scientists exploring the origins of life on earth were stymied by a basic question: Which came first, nucleic acids or proteins? Nucleic acids — DNA and RNA — carry each living thing's genetic code, the biological messages that tell it how to develop, grow, and reproduce.

However, in today's complex organisms nucleic acids cannot function without special proteins. Proteins control which segments of DNA are activated and which remain dormant. They unzip the double-stranded DNA molecule so that its code can be read by other proteins.

These assemble either duplicate strands of DNA for cellular reproduction or single-stranded RNA molecules which take the genetic message to other parts of the cell. Still other proteins are required to splice RNA, cutting out unnecessary segments and reconnecting the strand into an edited message.

By reconstructing the probable chemical conditions of a primitive earth, scientists were able to create a "primordial soup" containing the molecules required to build both nucleic acids and proteins. But for the transition between random chemical reactions and living organisms, they were left with proposing unlikely scenarios, such as a chance encounter between a nucleic acid and a protein able to react with it.

Then in the early 1980s Dr. Thomas Cech of the University of Colorado made a remarkable discovery. He found a form of RNA in a single-celled animal that was able to splice itself without a protein's help.

Dr. Cech called this molecule a ribozyme — *ribo-* from ribonucleic acid (RNA), and *-zyme* from enzyme, a substance that is able to produce an action in another molecule. The discovery provided strong evidence that RNA might be the nucleic acid in the first living cells and brought Dr. Cech the 1989 Nobel Prize.

"We now know that RNA molecules are unique because they have the dual capacity both to store information in their sequence and to catalyze reactions [to act as an enzyme]," Dr. Szostak said.

"This really makes it probable that RNA was the first nucleic acid. Eventually RNA enzymes developed that could make proteins, which then took over the specialized jobs they could do better. The evidence is very consistent with DNA's not developing until later."

Studying the activity of RNA enzymes and investigating their role in the evolution of primitive cells has been a major effort in Dr. Szostak's lab for several years. The team has developed several specialized RNA enzymes based on the ribozyme discovered by Dr. Cech.

Collaborating with Dr. Szostak during the project's early years was Jennifer Doudna, PhD. Currently his principal collaborator is Rachel Green, PhD.

"What we have now is an enzyme that can take several small RNA segments and string them together to make a strand that is complementary to a molecule we want to copy," he explained. A complementary strand is essentially a chemical mirror-image, one which would allow copying and reproduction of the original RNA strand.

The enzyme Dr. Szostak describes constructs a complementary strand using smaller RNA segments that already match the original strand — a process similar to reconstructing a message from scrambled words. What he and his colleagues ultimately hope to develop is an RNA enzyme that could build a strand from the individual molecular building blocks, like recreating the message letter-by-letter.

If they are successful in creating what would in essence be a self-replicating RNA, the next step would be putting that molecule into a cell-like environment. That task should be relatively easy.

The membranes that surround all cells and partition off their internal compartments are made primarily of fat molecules called lipids. Because fats — like oil — do not mix with water, lipid molecules introduced into a watery environment tend to clump together in several distinctive shapes.

One of these shapes is a hollow sphere made of a double layer of lipid cells, a

*(Concluded on Page 8)*

## — First Cells

*(Concluded from Page 7)*

structure called a liposome. If the self-replicating RNA were placed inside a liposome, along with the building blocks required to construct new RNA molecules, the result could be considered a very primitive cell.

The RNA population of these cells could increase with a continuous supply of molecular building blocks, perhaps provided by fusing the cells with "food"-carrying liposomes. Dr. Szostak explained that applying such external forces as shaking the liposomes or forcing them through tiny openings could cause large cells to break apart and reform into smaller ones — mimicking the process of cell division.

Could these cells be considered alive? Dr. Szostak thinks so. The RNA replication that would occur in these cells would be subject to errors, just as DNA replication is in a natural system. Errors would be transmitted to subsequent generations of cells.

Some errors might cause the replication process to break down. But occasionally a mutation conferring a benefit could occur. Cells with this mutation might grow faster or replicate more efficiently, conferring the kind of survival advantage that is basic to the process of natural selection.

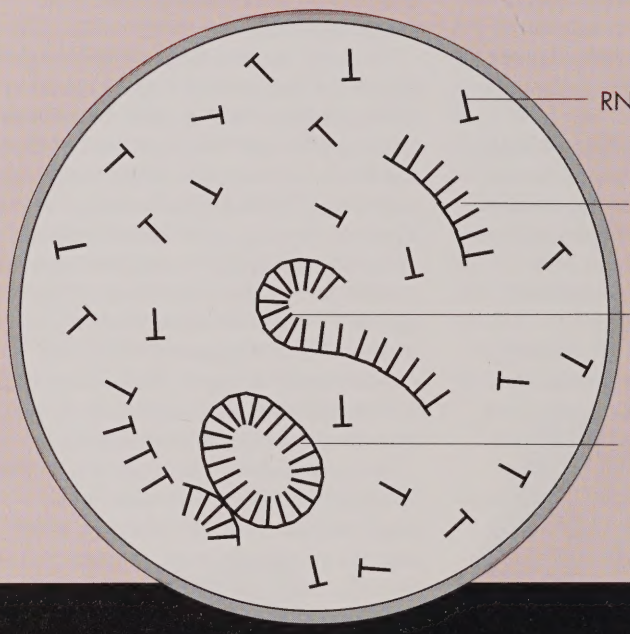
Dr. Szostak asserted, "I think a biological system that can change in a way that's inherited, so that the better variants reproduce more successfully, would qualify as being alive."

Alive they might be, but these cells would be far simpler than any naturally-occurring organisms, which have grown increasingly complex over four million years of evolution. They would be totally dependent on the artificial laboratory environment, where the researchers would control cell division and the activation of RNA enzymes.

"If these cells were released into the environment, they'd be immediately eaten up by bacteria," Dr. Szostak said. "They just couldn't compete with anything that exists now."

As in many scientific endeavors, much of what will be learned from these cells will come from the development process itself. Through trial and error, Dr. Szostak and his colleagues will learn more about the workings of RNA enzymes. Observing the molecules' evolution, they will see how subtle changes can result in beneficial or deadly (to the cell) mutations.

Should they succeed in creating primitive RNA-based cells, they may provide a window through time, back to the earliest stirrings of life itself. ■




***To recreate primitive cells, scientists are are using a special kind of RNA as genetic material. This RNA can both carry genetic information and can act as an enzyme — that is, it can stimulate the assembly of duplicate RNA strands.***

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